- ENGLISH -

STUDY INFORMATION AND INFORMED CONSENT FORM FOR PARENTS

- NAC TRIAL -

Reducing the incidence of daily life pain in patients with Sickle Cell Disease

Dear Sir / Madam,

Your child has been asked for participating in the above-mentioned medical research. This research will take place in four Dutch hospitals, namely the Academic Medical Center (AMC), the Erasmus Medical Center (EMC), the University Medical Center Groningen (UMCG) and the Haga Hospital. Furthermore, several hospitals in Belgium and the United Kingdom will participate in the study. A total of 140 patients (adults and children over 12 years) will be included for participation.

Before making a decision, it is important to be properly informed and consider the participation of your child. Therefore you have received this information letter. This decision is totally up to you and your child. Before you decide, it is important to know more about the research and to understand the potential risks, inconveniences and benefits of participation. Take your time to read this information. You have also received the brochure "Medical Research" of the Ministry of Health, Welfare and Environment. It contains a lot of general information about medical research.
You can also discuss this study with your partner, family or friends. The participation of your child is completely voluntary. If you have any further questions after reading this information, please contact one of the researchers that are mentioned at the end of this newsletter. In Appendix A you will find all contact details.

WHAT IS THE PURPOSE OF THIS STUDY?

Sickle cell disease is a condition that is characterized by frequent painful episodes (crises). Patients instantly have severe pain and sometimes need to be admitted in the hospital for pain treatment until the crisis is over. During these painful episodes damage to organs and tissues of patients can occur. In this study, we will investigate whether treatment with the drug N-acetylcysteine (NAC) can reduce the frequency of pain and painful crises in sickle cell patients.

We hope to answer the following questions:
• Do sickle cell patients have less pain and painful crises when using N-acetylcysteine daily?
• Are there less hospital admissions of patients?
• Do sickle cell patients have a better quality of life when using this drug daily?
• Are the social costs of care for these patients lower when using this drug?

WHAT TYPE OF DRUG WILL BE USED?

The drug that will be studied is N-acetylcysteine (NAC). This medicine has been registered for years for other diseases, for example as a cough medicine for respiratory disease.
Recent studies have shown that this drug may also be effective in treatment of pain in sickle cell disease. This is because NAC is also an antioxidant; an agent that can neutralize free radicals (substances that damage cells and tissues). These free radicals also seem to play an important role in the occurrence of pain in sickle cell disease.
NAC might therefore potentially reduce complaints of pain and painful crises in Sickle Cell Disease.

HOW WILL THIS STUDY BE PERFORMED?

This is a so-called randomized double-blind placebo study in which NAC will be compared to a placebo drug (inactive medication). Double-blind means that you, your child, the doctor and the researcher do not know which treatment your child gets. Treatments are assigned by lot (chance). You, your child, the doctor and the researcher have no effect on the results and on which agent your child will get. Half of the patients will receive NAC and the other half will receive placebo. The probability is about 50% that your child will get placebo and 50% that your child will get the active drug. This technique allows us to compare the results between the two groups as accurate as possible.

If you decide to let your child participate in this study, he/she will first start a screening period of 2 weeks. During this period your child is required to daily fill out a so-called pain diary. After these 2 weeks we will evaluate together if he/she was able to understand and fill out the diary. Subjects with insufficient registration in their diary subsequently are not able to participate in the study. After this screening period the randomization (assignment of treatments) will take place.

The medication will be given in outpatient department by the researcher. The drug is in tablet form and has to be taken twice daily. The entire treatment period will last six months. It is very important for this study that your child properly takes the study medication and accurately fills out the pain diary.

WHAT IS EXTRA OR DIFFERENT FROM THE TREATMENT YOUR CHILD NORMALLY GETS?

Normally your child comes about 1 time every half year for check-up. For this study it is required that during 6 months your child comes to the hospital every month. Among other things, your child will then receive a new supply of study medication. In total your child will have to come 5 extra times to the hospital. An appointment will last about 20-30 minutes every time.

The following other procedures will be performed specifically for this study:

<u>Pain Diary</u>

In order to properly assess the pain that patients with Sickle Cell Disease experience, it is very important that your child keeps a daily pain diary. Your child can specify here whether he/she had pain or not, and if so, how severe that pain was, whether it was a pain crisis, and if he/she used analgesia. Filling out the diary will take maximally 1 minute daily (only when there actually was pain, all the extra questions need to be completed). Your child will fill out the diary daily for 2 weeks during the screening period and for 6 months during treatment.

Blood tests

At the start of this study, after 3 and after 6 months, extra blood will be taken. Your child will only be punctured one extra time for this study on average as the other samples will be taken during blood drawing for regular check-ups. Per sample about 21 ml of extra blood (4 tubes) will be drawn compared to a normal.

Questionnaires

At the start of this study, after 3 and after 6 months, your child will be asked to fill out two short questionnaires. After 3 and after 6 months you will also be asked to fill out a questionnaire. We will use these questionnaires to evaluate the potential effects of the use of this study drug on the quality of life and social costs for care to sickle cell patients. Total duration for completing both questionnaires will take approximately 15-20 minutes. You can do this also at home.

SMS reminders

In order to help your child not to forget using the medication and completing the diary, we offer an SMS service. With the permission of you and your child we can send text messages on your and your child's mobile phone, free of charge, about 2 times a week as a reminder of his/her participation in the study. You will both have to give extra written consent for this by signing the special form in Appendix E. This service is not obligatory for participation in this study.

Appendix B provides an overview of all visits and investigations.

WHAT IS EXPECTED OF YOUR CHILD?

During this investigation your child will have to take the study medication 2 times daily during 6 months and fill out a daily pain diary.
We ask your child to follow the doctor's instructions. It is important that he/she comes for all the study appointments. If your child can not make it to an appointment, please contact the study contact person to make a new appointment. Furthermore, for your safety it is important that your child does not receive treatment or participate in another study without the knowledge of his/her doctor here. This is to protect your child, in case certain drugs can not be combined with the study medication. Pregnant patients or patients who are breastfeeding can not participate in the study. Therefore a pregnancy test will be performed in all female patients in fertile age. Women trying to get pregnant in the next seven months can also not participate in this study.

ALTERNATIVE TREATMENT OPTIONS

At this time, there is one other effective treatment for reducing the number of painful crises in sickle cell patients. This drug is called Hydrea / Siklos. It is prescribed in Sickle Cell Disease to patients with severe symptoms of the disease (frequent hospitalizations). This treatment has several disadvantages. In 1 out of 3 patients, the drug has no effect. Furthermore, there are patients that develop adverse reactions due to the drug and do not tolerate it.
If you are already using Hydrea / Siklos, you can also participate in this research.

SIDE EFFECTS

N-Acetylcysteine has been registered for years for treatment of other diseases, for example in cough for respiratory disease. It has been shown that taking this drug is very safe. The most important side effects known are gastrointestinal symptoms such as nausea, diarrhea and / or vomiting. These are rare though in the dosage that we will be using. The placebo (fake medication) contains no active substances and the risk of side effects is therefore minimal.

In this research there still is a risk of experiencing side effects or other inconveniences. We can not guarantee that no side effects will occur. Not all side effects are listed here. It is also possible that side effects will occur that are not yet known. If your child experiences any new symptoms, we ask you and your child to inform his/her physician. Even if you or your child think that it is not related to the study medication. In case of severe symptoms you and your child should immediately contact a doctor; Outside office hours please contact the pediatric haematologist on call of your hospital. In addition, during every study visit your child will be asked if he/she experienced any problems and if so, to what extent.

WHAT ARE POSSIBLE ADVANTAGES AND DISADVANTAGES OF PARTICIPATION IN THIS STUDY?

It is not certain whether your child will benefit directly of the study treatment. This study is meant to test a new treatment option for reducing attacks of pain in sickle cell disease.
It is possible that your child responds well and that he/she therefore experiences less symptoms. However, this is not certain and it is also possible that your child does not benefit from this treatment. Furthermore, this research will provide valuable information that can be important for future treatment of other patients with Sickle Cell Disease.
A disadvantage of this study can be that during half a year your child is required to visit the hospital monthly for check-up, that he/she has to take the medication 2 times per day and that he/she has to keep a daily pain diary.

VOLUNTARY PARTICIPATION

The decision to participate in this study or not is totally up to you and your child. Participation is voluntary. Whatever you and your child decide, it will not affect the treatment and care for your child, you or your family.
If you decide not to let your child participate, you don't have to do anything. You don't have to sign anything. You are not obliged to say why you do not want him/her to participate. Your child will just receive the treatment and care that he/she would normally get. If your child does participate, you and your child can always change your mind and quit anyway, without giving any reason. The doctor will then discuss with you and your child what treatment is best for him/her.
If your child wants to quit the study before the end, please notify the study doctor so we can safely end the study treatment.

WHEN IS THE STUDY COMPLETED?

The study ends after 6 months and 2 weeks. It is also possible that your child's doctor decides to stop the treatment before the end of the study, for example when he/she is experiencing too many side effects. The study can also be stopped beforehand when new information comes up about your child's illness or the study treatment.

INSURANCE

For anyone who participates in this study, insurance is provided by us. This insurance covers damage resulting from this research. This applies to damage that comes up during the study, or within four years after the end of the study. Information can be found in Appendix C.

ARE THERE ADDITIONAL COSTS OR IS THERE COMPENSATION INVOLVED WITH PARTICIPATION?

There are no costs for you or your child when participating in this study. Your child will not be paid or rewarded for participation. However, travel costs will be reimbursed.

WILL YOU AND YOUR CHILD BE INFORMED WHEN RELEVANT INFORMATION ABOUT HIS/HER DISEASE OR THIS STUDY COMES UP?

This research will be carried out according to protocol. It is possible that your child's doctor decides to stop treatment before the end of this study, for example because of medical reasons such as side effects. It is also possible that new information about your child's disease or study treatment is discovered. The chances that such things are found during this study are very small. When we find something, you and your child will be notified by your child's doctor. You and your child can then decide for yourself whether to stop or continue with the study. If the safety or well-being of your child is in danger, we will immediately stop treatment. With your and your child's permission, we will also inform the house doctor. If you or your child do not wish to be informed about the above mentioned events, he/she can not participate in the study.

WHAT WILL HAPPEN WITH YOUR CHILD'S STUDY DATA?

A few other people can see study data with your child's information. People who can see this include: the research team, the review committee and the Health Inspectorate. In addition, designees of the initiator of this research are allowed access to confidential data to check if this research is in agreement with protocols and regulations. All data and blood material that is collected during this study will be anonymously marked with a code number. Your or your child's personal information will not be provided in research documentation. Furthermore, in any publications personal data will not be stated. Only the person who has the key to the code knows who the patient is behind the code.

Blood material will be stored for up to 15 years after the end of the study and your child's medical study records will be kept for 20 years after conclusion of this trial. It is possible that we use study data or stored blood material in the future for research that is not described in this protocol. The future research should be an extension of the current research. Such additional research can also be conducted only if the Medical Ethics Review Committee has given approval again.

If you or your child decides to end his/her participation in this study prematurely, the research team will stop collecting data. You may request to destroy all of your child's previously collected samples. Materials that have not been used for analysis yet, will then be destroyed.

ADDITIONAL SCIENTIFIC RESEARCH

Additional research on blood material can teach us more about the characteristics of your illness and can help us improve diagnostic and treatment options in the future. We ask your and your child's permission to use his/her blood material for additional research in the future. Since that is additional scientific research, this means that the outcome of that research does not have any consequences for his/her current treatment and that your child will not directly benefit from this. Blood material that will be collected during this study, will be coded. This means that all personal data are removed. Researchers have no access to your child's personal data.
The stored blood will be stored for up to 15 years after the end of the study. If you or your child do not agree with storage of his/her blood for additional scientific research, the material will be destroyed upon completion of this investigation. This will not affect your child's participation in the study.

WILL YOUR CHILD'S HOUSE DOCTOR AND / OR SPECIALIST BE INFORMED OF HIS/HER PARTICIPATION?

If your child has a house doctor and / or specialist, the study doctor will inform him/her by letter that your child is participating in this study. This is for your child's own safety. You will give your consent for this on the consent form. If you do not agree, your child is not able to participate in this study.

APPROVAL

This research was reviewed and approved by the Medical Ethics Committee of the Academic Medical Center. The current international guidelines for this research will be followed closely.

DO YOU HAVE ANY FURTHER QUESTIONS?

Of course you need time to consider your child's participation in this study. You probably want to discuss the study with others. You have the opportunity to do so. If you have more questions after reading this information, you can discuss this with your child's doctor or the study doctor in the hospital.

If you are unsure about your child's participation in this research, you can also contact the independent doctor. This doctor is not involved in this study, but is an expert on this field and your child's illness. It is also possible to contact this doctor during the study, if you or your child have any questions that you'd rather not discuss with your child's own doctor or the study doctor.

If you are discontent with the investigation or treatment, you can file a complaint.
In Appendix A you will find the contact information.

SIGNING OF THE CONSENT FORM

If you decide to let your child participate in this study, we ask you to sign the consent form. By signing this consent form, you agree to let your child participate in this study. You can at any time withdraw your consent. Your child's doctor or the study doctor will also sign the consent form, confirming that you and your child are informed about the study and that you have received this mailing. You will receive a copy of the consent form along.

ANNEXES:

Appendix A: Contact information
Appendix B: Summary of study procedures and outpatient visits
Appendix C: Information on insurance
Appendix D: Study Consent Form Parents (in duplicate)
Appendix E: Consent form for SMS service

Separate Annex: General brochure Medical Research (Ministry of Health)

APPENDIX A: Contact information

You can get more information about this study with one of the doctors or researchers of the Academic Medical Center:

- Mrs. dr. K. Fijnvandraat, pediatrician-hematologist
  Tel: 020-5662727

- Drs. Joep Sins, coordinating physician-scientist
  Tel: 020-5661693 E-mail: j.w.sins@amc.nl

Independent physician
If you are unsure whether to let your child participate or not, you can contact the independent doctor, who is not involved in the investigation, but is an expert in the field of this study. Also if you have questions before or during the study that you prefer not to talk about to your child's doctor, you can contact the independent physician:

- Dr A.P. Kater, internist-hematologist
  Tel: 020-5665785.

Complaints
If you or your child are discontent or feel mistreated with the investigation or study treatment, you can report it to your child's doctor. If you rather wish not to discuss this directly with this doctor, please contact the "Department Patiëntenvoorlichting" of the Academic Medical Center. This department can be reached by phone: 020-5663355.

APPENDIX B: Summary of study procedures and hospital visits

TREATMENT

	-2 weeks	0 months	1 month	2 months	3 months	4 months	5 months	6 months
	Study initiation	**START**						**STOP**
	Screening	**Start treatment**						**End treatment**
Written consent for study participation	X							
Outpatient dept visits	X	X	X	X	X	X	X	X
Pain diary	Daily	Daily	Daily	Daily	Daily	Daily	Daily	Daily
Blood sampling		X			X			X
Questionnaires		X			X			X
Pregnancy test (for women in fertile age)		X						

APPENDIX C: Information on insurance

In accordance with the Dutch Medical Research (Human Subjects) Act (*Wet medisch-wetenschappelijk onderzoek met mensen*, WMO), AMC Medical Research B.V. has taken out an insurance cover for claims resulting from the death or bodily injury of human subjects of clinical trials.

* This concerns injuries that become apparent during the clinical trial or the four years immediately following said trial, and that have been reported within four years from the participation in the clinical trial.
* The sum insured under this policy is EUR450,000 per subject, with a maximum of EUR3,500,000 for the clinical trial project and EUR5,000,000 for injuries arising from medical research per insurance year.

The policy provides cover for:
* injuries resulting from the realization of risks attached to participating in a clinical trial, of which the participant had not been informed in writing;
* injuries resulting from the realization of risks, of which the participant had been informed, but which manifest themselves to a greater degree than expected;
* injuries resulting from the realization of risks of which the participant had been informed, but which were considered to be extremely unlikely.

The policy does not cover:
* claims resulting from a lack of improvement in the subject's health problems, or from a continued deterioration of the subject's health problems, if the subject's participation in this clinical trial is part of the treatment of this health problem;
* claims resulting from an impairment of the subject's health, which would likely also have come to light if the subject had not taken part in the research;
* claims resulting from an impairment of the subject's health in case the subject takes part in a comparative clinical trial and it is likely that the injury results from procedures that are already commonly used in the medical profession;
* claims for injury that manifests itself in the subject's descendant as a result of an adverse effect of the clinical trial on the subject and/or his/her descendant;
* claims for injury that is inevitable or practically inevitable, given the nature of the clinical trial;
* claims for injury resulting from the subject's own failure to follow the instructions, or to follow them completely, insofar as the subject is able to do so.

The policy covers losses of individuals only.

The cover of specific injuries and costs is limited to the amounts stipulated above.

To lay claim to damages, the subject has to report the putative injury as a result of the clinical trial to:

Name of insurer:	Centramed B.A.
Address insurer:	Appelgaarde 4, 2272 TK Voorburg
Policy number:	620.872.806
AMC Contact:	Mrs. Ruiter, tel: 020-5665558

APPENDIX D:

STUDY CONSENT FORM FOR PARENTS

Reducing the incidence of daily life pain in patients with Sickle Cell Disease

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- I have read the study information for parents of patients, version 3.0. I understand the information. I was able to ask additional questions. My questions have been answered satisfactorily. I have had sufficient time to decide whether to let my child participate or not.
- I hereby give my consent for the participation of my child in the above mentioned medical scientific research.
- I know that his/her participation is completely voluntary. I may at any time decide to withdraw my consent and his/her participation without having to give any reason for this.
- For quality and reliability assessment of this study, I hereby give my permission for access to my child's personal information regarding this study to representatives of the Health Care Inspectorate (IGZ) and representatives of the initiator of the study.
- I give permission to inform my child's house doctor and treating specialist(s) on my child's participation in this study.
- I give permission to process the data for the purposes described in this information letter.
- I give permission for the storage of my child's personal data (coded) for up to 20 years after completion of the study.

I **give / do not give*** consent to store my child's blood for up to 15 years after the end of this study so that it may be used for future additional research purposes.

I **give / do not give*** consent to let my child be contacted in the future for further research.

|_____| Name participant **		|__|__| - |__|__| - |__|__|__|__| Date of birth **
|_____| Name (parent1/lawful guardian1) **	|___-____-____| Date **	|_____| Signature
|_____| Name (parent2/lawful guardian2) **	|___-____-____| Date **	|_____| Signature

I hereby declare that I have fully informed the parents or lawful guardians of the subject about the mentioned study. If during the research information comes available that could affect the consent of the parents or guardians, I will inform them timely.

|_____| Name Research Employee**	|___-____-____| Date **	|_____| Signature

** Please strike out whatever answer is not applicable*
*** Please use block letters. Note the date in the following way: dd-mm-yyyy.*

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|_____| Name participant **		|__|__| - |__|__| - |__|__|__|__| Date of birth **
|_____| Name (parent1/lawful guardian) **	|___-____-____| Date **	|_____| Signature
|_____| Name (parent2/lawful guardian) **	|___-____-____| Date **	|_____| Signature

I hereby declare that I have fully informed the parents or lawful guardians of the subject about the mentioned study. If during the research information comes available that could affect the consent of the parents or guardians, I will inform them timely.

|_____| Name Research Employee**	|___-____-____| Date **	|_____| Signature

** Please strike out whatever answer is not applicable*
*** Please use block letters. Note the date in the following way: dd-mm-yyyy.*

APPENDIX E:

CONSENT FORM SMS SERVICE

Reducing the incidence of daily life pain in patients with Sickle Cell Disease

I give permission to receive free text messages on my and my child's mobile phone during the course of this study for the purpose of reminding participants of medication use and use of the pain diary.

Name participant: _____

Date of birth: |___|___| - |___|___| - |___|___|___|___|

Date: |___|___| - |___|___| - |___|___|___|___|

Name parent/guardian 1: _____

Signature: _____

Name parent/guardian 2: _____

Signature: _____

Mobile phone number parent: |___|___| - |___|___|___|___|___|___|___|___|