PARTICIPANT INFORMATION SHEET

- NAC TRIAL -

N-Acetylcysteine (NAC) in sickle cell disease; Reducing the incidence of daily life pain

Dear Sir / Madam,

We would like to invite you to take part in the above mentioned research study. In this study we aim to investigate whether treatment with the drug N-Acetylcysteine can **reduce** the frequency of **pain** and painful crises in patients with **sickle cell disease**.
This study will take place in the Guys' and St. Thomas hospitals in London. Furthermore, several hospitals in the Netherlands and Belgium are also participating in this study.

Before you decide we would like you to understand why the research is being done and what it would involve for you (potential risks, inconveniences and benefits). **One of our team will go through the information sheet with you and answer any questions you have**. We'd suggest this should take about 20 minutes. Talk to others about the study if you wish.

- **Part I** tells you the purpose of this study and what will happen to you if you take part.
- **Part II** gives you more detailed information about the conduct of the study.

Your participation 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.

On **page 7** you will find further **contact** information.

NAC trial – local information	
Study center:	**Guy's and St Thomas NHS Foundation Trust** Clinical Haematology 4th Floor, Southwark Wing Great Maze Pond London - SE1 9RT
Investigator:	Dr. R. Kesse-Adu
If you have any questions about this study, you can contact:	
Daytime:	Sarah El Farhi / Karen Amaradivakara on 0207-1884259
Out of hours /	Guy's and St Thomas' Foundation Trust (GSTFT)
Emergency:	Switchboard, Telephone: 020-7188-7188 and ask to be connected to the On-Call Hematology Registrar.

PART I

WHAT IS THE PURPOSE OF THIS STUDY?

Sickle cell disease is characterized by frequent painful episodes (crises). Patients instantly suffer from severe pains. Sometimes they need to be admitted in the hospital for pain treatment until the crisis is over. In this study we will investigate whether daily treatment with the drug N-acetylcysteine (NAC) can reduce complaints of pain in sickle cell disease.

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?

WHY HAVE I BEEN INVITED?

For this study we ask all adult patients with sickle cell disease in our hospital if they wish to participate. Furthermore, we are also recruiting patients in hospitals in the Netherlands and Belgium. In total, we aim to include a maximum of 140 patients.
Patients receiving chronic blood transfusions cannot participate.This is because transfusions may also reduce the frequency of pain in sickle cell disease.

DO I HAVE TO TAKE PART?

The decision to participate in this study or not is totally up to you. Participation is **voluntary**. We will describe the study to you and go through this information sheet. If you agree to take part, we will then ask you to sign the consent form. You are free to withdraw from the study at any time, without giving a reason. This would not affect the standard of care you receive.

If you decide not to participate, you don't have to do anything. Whatever you decide, it will not affect the treatment and care for yourself and your family.

WHAT TYPE OF DRUG WILL BE STUDIED?

The drug that will be studied is called **N-acetylcysteine** (**NAC**). We have wide experience with this medicine. It has been registered and used for years in other diseases. For example, it is used as a cough medicine in lung disease. It has proven to be safe here.

Recent research has shown that this drug may also be effective in sickle cell disease. This is because NAC is an **antioxidant**. Antioxidants are agents that can help the body neutralize so-called "free radicals". These "free radicals' are substances that damage cells and tissues.There are many types of antioxidants. Some are used as dietary supplements, just like vitamins. In sickle cell disease the damaging free radicals appear to be involved in the occurrence of pain .
We think that the antioxidant NAC may reduce complaints of pain in sickle cell disease by neutralizing these free radicals.

See **appendix B** for more information on the study drug.

WHAT WILL HAPPEN TO ME IF I TAKE PART?

HOW WILL THIS STUDY BE PERFORMED?

The main goal of this study is to assess the effectiveness of the drug NAC. The best way to do this is by means of a so-called "randomized double-blind placebo study". This means that in this study we will **compare** NAC with a placebo drug (inactive medication) to see if one is better.

One of these treatments is assigned to you by lot (chance). Both you, your doctor and the researcher do not know which treatment you get. We call this "double blind". You, your doctor and the researcher have no effect on this. In total, half of the participants will receive NAC and half will receive placebo. Therefore, the probability is about 50% that you will get the placebo and 50% that you will get the real, active drug.
This method allows us to compare the frequency of pain between these 2 groups in the best and most unprejudiced way.

WHAT PROCEDURES ARE INVOLVED WITH PARTICIPATION?

If you decide to participate , you will first start a **screening period** of 2 weeks. During this period you are asked to fill out a short, daily pain diary. After these 2 weeks we will evaluate together if you were able to understand and keep the diary. If you had insufficient registration in your diary , it isnot possible to continue with the study. After this screening period theassignment of treatments ("randomization") will take place. At this point the study medication will be administered.

You will receive the study medication in outpatient department from the researcher. The drug is in tablet form and has to be taken by mouth twice daily during a total of 6 months. After these 6 months, the study is finished. It is very important for this study that you take your study medication properly and accurately fill out the pain diary. In total, you will thus participate for **6 months and 2 weeks**.

See **appendix A** for a flowchart of the study.

WHAT IS EXTRA OR DIFFERENT FROM THE TREATMENT I NORMALLY GET?

Normally you come about once every half year for check-up. For this study it is required that during your participation you come to the hospital every month. In total, you will thus 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:

- ***Pain Diary***
  For the study it is very important that you keep the **daily** pain diary. This allows us to assess the pain that participants have during their participation.
  In the diary you can specify whether you had pain or not, and if so, how severe that pain was, whether it was a painful crisis, and if you used any pain medication. Filling out the diary will take maximally 1 minute per day. You will need to 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 samples will be taken (see flowchart in appendix A). You will only be punctured one extra time for this study on average. We aim to draw the other samples during blood drawings for regular check-ups. Per sample about 21 ml of extra blood (4 tubes) will be drawn compared to normal.

- ***Questionnaires***
  At the start of this study, after 3 and after 6 months, you will be asked to fill out two short questionnaires. We will use these questionnaires to measure the effectsof this study drug on the way participants feel about their health. Also, we will assess the effects on societal costs for sickle cell disease care. Total duration for completing both questionnaires will take approximately 15-20 minutes. You can also do this at home.

- ***Text message reminders***
  In order to help you remind taking the medication and completing the diary, we offer an SMS text message service. With your permission and **free of charge**, we can send you text messages on your mobile phone about **2 times a week**. This is to remind you of your participation in the study. You will have to give separate consent for this on the consent form. This service is **not** obligatory for participation in this study.

Appendix A provides an overview of all visits and investigations.

EXPENSES AND PAYMENT

There are **no expenses** for you when participating in this study. Travel costs for extra hospital visits can be **reimbursed**. You will not be paid or rewarded for participation.

WHAT IS EXPECTED OF ME?

During your participation you will have to take the study medication 2 times daily during 6 months and fill out a daily pain diary. Also, 3 blood samples will be drawn and you will fill out three questionnaires.It is important that you come to all your appointments. If you cannot make it to an appointment, please contact the study contact person to make a new appointment.

We ask you to follow your doctor's instructions. For your safety it is important that you do not receive treatments or participate in other studies without the knowledge of your doctor here. This is for your own safety.
Pregnant patients or patients who are breastfeeding **cannot** participate in the study. Women planning to get pregnant in the next 7 months can also not participate in this study. Therefore, a pregnancy test will be performed in all female patients in fertile age. Also, an effective form of birth control is required during participation. In case of a new pregnancy during the study or questions about effective birth control, please consult your physician or the research staff.

WHAT ARE THE ALTERNATIVES FOR STUDY TREATMENT?

At this time, there is one effective drug for reducing complaints of pain in sickle cell disease. This drug is called **Hydrea / Hydroxycarbamide**. It is prescribed to patients with severe symptoms of the disease, for examplefrequent hospitalizations. This treatment has several disadvantages. In 1 out of 3 patients, the drug does not work. Furthermore, some patients experience side effects of the drug and do not tolerate it.
If you are already using Hydrea / Hydroxycarbamide, you can also participate in this research (if you still suffer from regular sickle cell pains).

WHAT ARE THE POSSIBLE ADVANTAGES, DISADVANTAGES AND RISKS OF TAKING PART?

It is not certain whether you will **benefit** directly of the study treatment. This study is designed to test a new treatment option to reduce pain in sickle cell disease. It is possible that you respond well and that you therefore experience less symptoms. However, this is not certain.It is also possible that you do not benefit from this treatment. You may also receive the placebo drug. In that case, no effect can be expected either. However, in any case this research will provide valuable information that can be important for future treatment of other patients with sickle cell disease.

Disadvantages of participation in this study can be that during 6 months you are required to visit the hospital monthly, that you have to take extra medication daily and that you have to keep a daily pain diary.

The **risks of participation** are estimated to be negligible. The study drug NAC has been registered for years and has proven to be safe.

WHAT ARE THE SIDE EFFECTS OF THE STUDY TREATMENT?

NAC has been registered for years for treatment of other diseases, for example for cough in lung disease. In these patients it has been shown that this drug is very safe. Possible side effects are well known and mild, especially at the dose used in this study.

The following **side effects** have been described:

- Abdominal discomfort, nausea, diarrhea and / or vomiting (infrequent, occurring in ca. 1 in 100 to 1.000 users)
- Hypersensitivity reactions resulting in itching, skin rash, respiratory discomfort (dyspnoea), dizziness and / or swelling of body parts (infrequent, occurring in ca. 1 in 100 to 1.000 users)

We cannot 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 you experience any new symptoms, we ask you to inform your physician. Even if you think that your complaints are not related to the study medication. The placebo (fake medication) contains no active substances and the risk of side effects is therefore minimal.
In case of **severe symptoms**, you should immediately contact your doctor; Outside office hours please contact the haematologist on call of your hospital. In addition, during every study visit you will be asked if you experienced any problems and if so, to what extent.
For **contact information,** please see **page 7** or consult **the label of the study medication.**

WHAT HAPPENS WHEN THIS STUDY STOPS?

The study ends after 6 months and 2 weeks. It is also possible that your doctor decides to stop the treatment before the end of the study. This may happen for example when you are experiencing too many side effects. The study may also be stopped beforehand when new information comes up about your illness or the study treatment.When the study stops, the use of the study medication and pain diary will be discontinued.

The study treatment will not be directly available for personal use after the end of the study. The results of this study will first have to be awaited. We can inform you about the treatment you received (NAC or placebo) only when all required participants have completed the trial.

WHAT IF THERE IS A PROBLEM?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in **Part II**.

WILL MY TAKING PART IN THE STUDY BE KEPT CONFIDENTIAL?

Yes, we will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in **Part II**.

*If the information in Part I has interested you and you are considering participation, please read the **additional information** in **Part II** before making any decision.*

PART II

WHAT IF RELEVANT, NEW INFORMATION BECOMES AVAILABLE?

It is possible that new and relevant information about your disease or the study treatment is discovered. The chances that such things are found during this study are very small. If we find something, you will be notified by the research doctor. You can then decide for yourself whether you want to stop or continue with the study.

If your safety or well-being is in danger, we will immediately stop treatment. If you decide not to carry on, your research doctor will make arrangements for your standard of care to continue. If you do not wish to be informed about the above mentioned events, you cannot participate in the study.

WHAT WILL HAPPEN IF I DON'T WANT TO CARRY ON WITH THE STUDY?

You are **free to withdraw at any time**, without giving a reason. This would not affect the standard of care you receive. Please contact your doctor in this case. Your participation will then be discontinued safely. Of course, we hope that all participants complete the study as this is best for the study results.
If you decide to end your participation in this study prematurely, you can withdraw from the study. However, please do inform us about your progress. Information collected about you for the study may still be used. Any previously collected blood samples that can still be identified as yours, can be destroyed if you wish.

WHAT IF THERE IS A PROBLEM?

Every care will be taken during the course of the study. If you have a **concern** about any aspect of this study, you should ask to speak with the researchers: **Dr. R. Kesse-Adu** or **Dr. J. Howard** on **0207-188-2741** or **0207-188-4259**. They will do their best to answer your questions.

If you remain unhappy and wish to complain formally, you can do this through the **NHS Complaints Procedure**. Additional information is available from your local Patients Advice and Liaison Service Office on telephone numbers 0207-188-8801 or 020-7188-8803 or www.pals.nhs.uk/.

During the study, if there is an **emergency** please contact the **on-call hematology registrar** through the hospital switchboard on **020-7188-7188**. If you have to visit another doctor, please make sure you tell that person that you are taking part in this trial. They can contact your research doctor if necessary.

For your safety, we will keep one copy of this document with the study records of this trial. We will place a second copy in your hospital records. We will give you a third copy to keep.

HARM

The sponsor of this study, the Academic Medical Center in the Netherlands, holds an insurance policy which applies to this study. They will provide **compensation for any injury** caused by taking part in this study in accordance with the guidelines of the Association of the British Pharmaceutical Industry (ABPI).

We will pay compensation where the injury probably resulted from

- A drug being tested as part of the trial protocol
- Any test or procedure you received as part of the trial

We would not be bound by these guidelines to pay compensation where;

- The injury resulted from a drug or procedure outside the trial protocol
- The protocol was not followed.

WILL MY TAKING PART IN THIS STUDY BE KEPT CONFIDENTIAL?

All data and blood material that is collected during this study will be **anonymously** marked under a code number, and stored in a secure database. Your personal information (e.g. name, address) will **not** be provided in research documentation. Furthermore, in any publications your personal data will **not** be stated. These **anonymized** data will be transferred **outside the UK** to the sponsor of this study; the Academic Medical Center in the Netherlands. **Only local research staff** will have access to the code and can identify the patient from this code.

A few other people can see study data with your information, and have access to collected samples. People who can see this include: the research team, regulatory authorities and the R&D audit (for monitoring of the quality of the research). All data and blood samples collected will be used for the purpose of this study only, as described in this information sheet.

Your medical records will be kept for **20 years** after the end of this trial. It is possible that we use anonymized study data in **future research** that is not described in this information sheet. The future research should be an extension of the current study. Such additional research can be conducted only if the leading research ethics committee in the Netherlands has given its approval again.

Blood samples may be used for future, additional research as well. You will be asked to indicate on the consent form if you give your **separate** permission for the storage and analysis of your samples in future research studies, subject to NHS Ethical Review. If you do not consent for the use of blood samples in future research, samples will be destroyed after completion of this study. If you do consent, (coded) blood samples will be stored by the sponsor for up to 15 years after the end of the study. After these terms data and samples will be disposed of securely.

What will happen to any samples I give?

Samples will be stored locally **under a code**, as described above. After completion of the trial, these anonymized samples will be transferred outside the UK for further analyses, to the sponsor of this study in the Netherlands.

WILL MY GENERAL PRACTITIONER (GP) / FAMILY DOCTOR BE INFORMED?

Your GP will be informed by letter by the research staff that you are participating in this study and that you will be using extra medication for the duration of the study. This is for your own safety. You will give your consent for this on the consent form. If you do not agree, you are not able to participate in this study.

WHAT WILL HAPPEN TO THE RESULTS OF THE RESEARCH STUDY?

The scientific results of this study will be published in international, scientific, medical journals. Personal information will **never** be stated. You will also be informed about the final results by your doctor or research staff, after full completion of the study.
Specific results with relevance for you as a patient will be communicated by your doctor.

WHO IS ORGANISING AND FUNDING THE RESEARCH?

This research is organised by the Academic Medical Center in Amsterdam (University of Amsterdam). Funding is provided by the Netherlands Organisation for Health Research and Development (ZonMw) and the Academic Medical Center, and by private funding by Fonds NutsOhra and the Janivo foundation (The Netherlands). There is no conflict of interest in this study.

WHO HAS REVIEWED THE STUDY?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by the London Fulham Research Ethics Committee.

FURTHER INFORMATION

You can find more general information about scientific research and clinical trials, please visit http://www.nhs.uk/Conditions/clinical-trials/.

If you have more questions specifically about this research after reading this information or if you would like to be advised on participation, you can discuss this with your doctor or the research staff in your hospital. All contact information can be found on **page 7**.

SIGNING OF THE CONSENT FORM

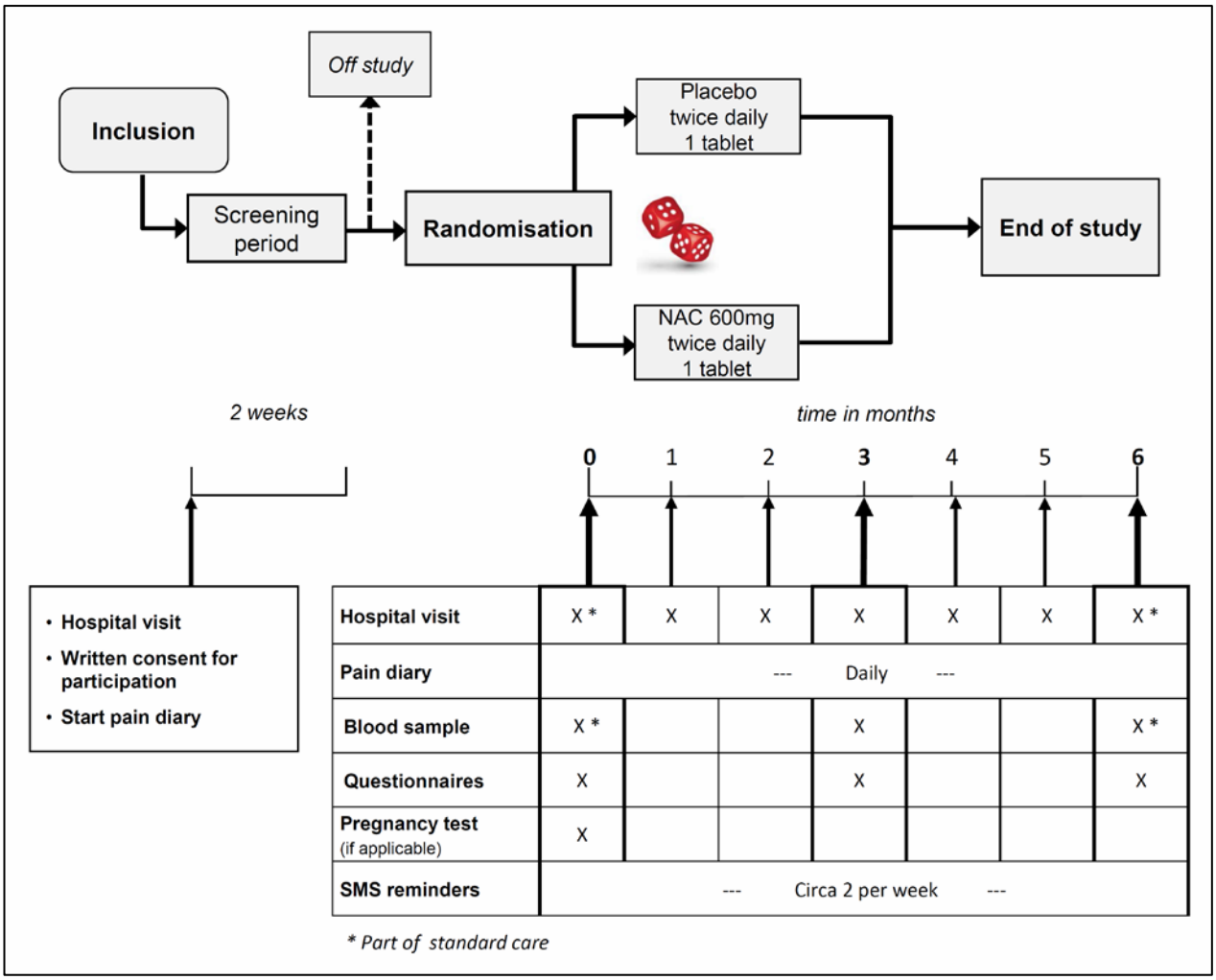
If you decide to participate in this study, we ask you to **sign the consent form**. By signing this consent form, you agree to participate in this study. You can **at any time withdraw** your consent to participate.

Your doctor or the study doctor will also sign the consent form, confirming that you 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: Summary of study procedures and outpatient visits
Appendix B: Additional information on study drug N-acetylcysteine (patient information leaflet)

APPENDIX A: Summary of study procedures and hospital visits



APPENDIX B: Additional information on study drug N-acetylcysteine

Patient Information Leaflet - N-acetylcysteine

1. **What is N-acetylcysteine and how does it work?**
   N-acetylcysteine increases the amount of a substance called glutathione in the body, which is a major antioxidant. This has been shown to help protect the body from the harmful effects of e.g. inflammation.

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2. **How should I take or use N-acetylcysteine?**
   N-Acetylcysteine tablets should be taken orally, preferably after food. If you are also taking antibiotics a gap of 2 hours should be left between taking a dose of acetylcysteine and taking a dose of antibiotic.
   The tablets should be stored in the original packaging, at room temperature, in a dry place.

3. **When shouldn't I use N-acetylcysteine?**
   - Do not take or use this medicine if you have previously had a **reaction** to N-Acetylcysteine, or during pregnancy or breast-feeding.
   - Take extra care if you have recently had a stomach/duodenal **ulcer** or have liver disease or phenylketonuria.
   - Please **tell your doctor** if you have either of these conditions.

4. **Are there any side effects?**
   It is well known that some medicines can cause side effects. N-acetylcysteine can sometimes cause diarrhoea, nausea and vomiting and possibly dizziness. Contact your doctor if these side effects carry on for more than a few days or make you feel worse.
   More rarely, patients may suffer an allergic reaction to N-acetylcysteine. This may cause a rash or possibly cause swelling in the mouth and throat making it difficult to breathe. If you have any of these effects, stop taking N-acetylcysteine and contact your doctor as soon as possible. See also page 5-6 of this information sheet.

5. **Will N-acetylcysteine affect any other medicines?**
   N-acetylcysteine is not known to affect any other medications. Tell your GP, dentist or pharmacist about all the other medicines you take. This includes any medicines you have had prescribed by another doctor as well as medicines bought from a pharmacy or supermarket
   and any herbal remedies.

6. **Can I drink alcohol while I am taking N-acetylcysteine?**
   Yes, it safe to drink alcohol while you are taking N-acetylcysteine. However, you should remain within recommended limits of 14 units a week for women and 21 units per week for men.

7. **How to store N-acetylcysteine**
   N-acetylcysteine should be:
   - Stored in the original packaging in a cool, dry place (below $25C^0$), away from direct sunlight;
   - Used before the manufacturers expiry date;
   - Stored out of the reach of children.

This leaflet is an adapted version based on the patient information leaflets 'N-Acetylcysteine' of the 'Doncaster and Bassetlaw Hospitals NHS foundation trust' (WPR32830 - July 2010) and 'Acetylcysteine (Fluimucil®) 600mg Effervescent Tablets' of the Worcestershire Acute Hospitals NHS Trust (WAHT-CG-611, version 1.1, 30th October 2015)