MONTEFIORE MEDICAL CENTER
ALBERT EINSTEIN COLLEGE OF MEDICINE

DOCUMENTATION OF INFORMED CONSENT AND HIPAA AUTHORIZATION

STUDY TITLE: A Phase II study of topical sodium nitrite for the treatment of leg ulcers in patients with sickle cell disease

Introduction

You are being asked to participate in a research study called **Leg Ulcer Study**. Your participation is voluntary. It is up to you whether you would like to participate. It is fine to say "no" now or at any time after you have started the study. If you say "no," your decision will not affect any of your rights or benefits or your access to care.

The researcher in charge of this project is called the "Principal Investigator."
Her name is **Dr. Caterina Minniti**.
You can reach Dr. Minniti at:
3411 Wayne Avenue
Suite A, Ground floor, Hematology
Bronx, NY 10467
Office: (718) 920-4137/4180
For questions about the research study, or if you believe you have an injury, contact the Principal Investigator or the IRB.

Support for this research study is provided by
The Food and Drug Administration (FDA).

The Institutional Review Board (IRB) of the Albert Einstein College of Medicine and Montefiore Medical Center has approved this research study. The IRB # is in the stamp in the upper right hand corner. If you have questions regarding your rights as a research subject, you may contact the IRB office at (718) 430-2253 or by mail:

Einstein IRB
Albert Einstein College of Medicine
1300 Morris Park Avenue, Belfer Building #1002
Bronx, New York 10461

Why is this study being done?

Chronic leg ulcers are a weakening side-effect of Sickle Cell Disease, in which red blood cells break down earlier than normal and can stick to vessel walls, causing a blockage that slows or stops the flow of blood. Current therapies are not very effective and often leg ulcers take months to years to heal.

We are doing this study to find out if a research cream made with nitrite, a substance that is known to increase blood flow by widening the surrounding blood vessels, is effective in reducing the time that it takes for the ulcer to heal and also if it has any bad side effects. We also want to see if it helps with the pain that often accompanies sickle cell ulcers. We are comparing the effects of research nitrite cream to a placebo. A placebo is an inactive substance. It looks like the research cream, but contains no medication. Researchers use placebos to find out if the study treatment is better than receiving no other treatment at all.

Nitrate cream has not been approved by the FDA for the treatment of chronic leg ulcers and is experimental in this study.

Why am I being asked to participate?

You are being asked to participate in this study because you have sickle cell disease and have one or more ulcer(s) on your leg or foot.

How many people will take part in the research study?

You will be one of about **40** people who will be participating in this study at the Montefiore Medical Center.

- 20 patients will use nitrite cream
- 20 patients will use placebo

How long will I take part in this research?

It will take you up to 14 weeks to complete the treatment phase of the study. During this time, we will ask you to make several study visits to Montefiore Health System of approximately two to three hours each, during the treatment phase you may come in twice a week for 10 weeks. The blood specimens will be used for research and genetic testing, your medical history, clinical evaluation records, and the data from questionnaires will be stored for an unlimited period of time.
After the treatment period, you will either come for monthly visits or will be called monthly for an additional six months, to evaluate long term effect of topical sodium nitrite on the host and the ulcer (how many ulcers re-open, close or remain closed). Thereafter, you will be followed up with phone calls once a year for 2 additional years.

What will happen if I participate in the study?

Screening visit

If you agree to participate in the research study by signing this consent form, you will be screened and evaluated to see if you are eligible to participate in this trial, by confirming your diagnosis of sickle cell disease, obtaining a methemoglobin level (to exclude congenital methemoglobinemia), a G6PD quantification (to exclude G6PD deficiency), and Urine beta-HCG in reproductive age group females. A wound care doctor or nurse will check your ulcer(s) and measure them to ensure eligibility.

Initial visit

examination, baseline blood tests will be obtained. You will be asked to complete a series of questionnaires. The questionnaire asks about your feelings of discomfort or pain during the day, your quality of life and your ulcer history. Your ulcer(s) will be photographed and measured. You will be asked to provide a collection of saliva and a blood sample for PAX gene during the two weeks. Research blood and lab tests will also be obtained and the ulcer microbiome samples will be collected.

Run in period

You will receive at least two weeks of “standard of care” wound care, as determined by the wound care doctor or nurse and the PI, known as the “run-in period”. We will provide regular standard, medical wound care. This is done to see if regular wound care is sufficient to make the wound shrink. The total ulcer surface will be measured-at the end of this period. If standard wound care is sufficient to make the wound shrink by more than a quarter, you will not be able to continue with cream application. Otherwise, you will be randomized to receive sodium nitrite cream or placebo, and then you may come twice a week for 10 or more weeks.

Optional Punch Biopsy: One small piece of skin will be taken from the one of ulcers if you consent. The biopsy is optional; you can still participate in the study even if you elect not to have the biopsy.

INITIAL YOUR CHOICE BELOW
I consent to have an ulcer biopsy
Yes _____
No _____

Biopsy
If you consent, we will perform a **3-4 mm skin biopsy** at the edge of the ulcerated area. If you have multiple ulcers, the surgeon/wound care expert will decide which one is safest to biopsy. First you will be given lidocaine HCl to numb the area and reduce the pain. Then a small cut will be made in the skin. After the biopsy, your skin will be looked at under the microscope for:
a) bad blood supply
b) signs of inflammation
c) possibility of infection

Cream application and Dosing

You will be randomized (like flipping coin) to receive the **research cream** or the **placebo**. You will not know if you are getting the research cream or the placebo. The study doctor and study team will not know if you are getting the research cream or the placebo. You will have the cream applied to the ulcer on your leg twice a week for 10 weeks. Each time you come to the hospital during this period your leg ulcer(s) will be cleaned and the research cream or standard of care treatment will be applied. Every study visit the following steps will be taken:

Vital signs: Your vital signs (blood pressure, oxygen level and heart rate) will be measured at several intervals for 5 hours after the first application of research cream or placebo cream. If there are no issues with your vitals, we will measure them only once one hour after each cream application.

Blood Draw: Blood (approximately 149.5-179.5ml over 12 weeks = 11-13 tablespoons of blood) will be drawn from a vein in your arm for laboratory tests or an indwelling vascular catheter if already in place.

Wound Assessment: A wound care doctor or nurse will check your leg ulcer, measure its size, and take pictures. Microbiome samples will be obtained with swabs for each wound.

Pain Assessment and Qualify of Life Questionnaire: You will be asked to answers some questions about your quality of life through ASCQ-me, PROMIS, Beck Depression Inventory (BDI), Brief Pain Inventory (BPI) questionnaire and of your feelings of discomfort or pain during the day using a pain assessment tool (VAS assessment). VAS scale will be administered with each application of the study cream. If there is more than one ulcer, an individual VAS scale will be administered for each ulcer.

Mid-Study Dose Adjustment

After about 5 weeks on study, we will measure your wound size and: the sodium nitrite dose may need to be modified according to this scheme:

a) If, after 10 applications, a subjects' ulcer surface is decreased by more than 50% of the original area, we will decrease the dose by 50% for the remaining applications.
b) If, after 10 applications, a subject's ulcer(s) increases by 50% of the original area, we will increase the dose by 50% for the remaining applications.

End of study: You will return the week after the last application to have the study cream removed and perform end of study procedures. Vital signs including blood pressure and pulse oximetry will be measured. The surface area of all ulcerated surfaces will be measured and photographed with defined lighting, distance, exposure. The wound doctor or nurse will remove the "study cream" and obtain a repeat microbiome sample and research blood. Pain assessment: a VAS scale and ASCQ-me, PROMIS questionnaire will be administered. Laboratory tests to be obtained at End of Study include: CBC with differential and reticulocyte count, urinalysis with microalbuminuria, liver profile, electrolytes, LDH, CRP, and ESR.

Below is a table to explain the parts of the study:

Table 1: Sodium Nitrite Study Visit Schedule														
	Screening	**Baseline**	**Run-in**	**Double-Blinded Study Treatment Phase**										**EOS**
Visit Number	0	1	2	3-4	5-6	7-8	9-10	11-12	13-14	15-16	17-18	19-20	21-22	23
Week on Study Intervention		Week ~-2	Week ~-1	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11
Assessment Window	-	-	-	± 3 d	± 3 d	± 3 d	± 3 d	± 3 d	± 3 d	± 3 d	± 3 d	± 3 d	± 3 d	± 3 d
Study Procedure														
Informed Consent	x													
Basic Contact Info	x													
Demographics	x													
Medical History	x													
Beck Depression Inventory														x
ASCQ-Me														x
PROMIS														x
Brief Pain Inventory			x											x
Concomitant Medications				xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	x
Vital Signs	x	x	x	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	x
Baseline Physical Exam		x												
Non-Baseline Physical Examination	x							v11						x
MetHb	x					v7		v11		v15		v19		
G6PD	x[a]													
Hb Electrophoresis	x[b]													x
Baseline and EOS Labs		x												x
Monitoring Labs				x			v9		x		v17			
Research Labs (3 tubes)		x												x
Saliva for DNA Analysis		x												
Urine Pregnancy Test*		x												x
Randomization				v3										
Application of Cream				xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	
Wound Care		x	x	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	x
Ulcer History	x													
Ulcer Assessment	x	x	x	xx	xx	xx	xx	xx	xx			xx	xx	x
Ulcer Photography		x	x	x										x
Ulcer Biopsy			x											
Ulcer Microbiome			v2											x
Dose Modification										v13				

*: For women of childbearing potential only

xx: Twice per week assessment

a: If the subject had documented normal G6PD and metHb lab results, then no need to repeat

b: Only if no results available within 3 months

€: Screening and baseline can be combined into one visit

After the first three subjects have completed the study, if there are no significant side effects, especially significant changes in BP,

patients will be offered the option of applying the second weekly dose of the cream at home, by themselves or by a home health nurse.

Are there any risks to me?

Research Cream: You may feel stinging or a burning sensation around the site where the research cream is applied, which may require an increase in your normal pain medication. Your blood pressure may become low or you may develop swelling in your legs. Nitrite can change your hemoglobin to a form called methemoglobin, which does not bind oxygen. If there is too much methemoglobin, you may feel short of breath. We will test your blood frequently for this side effect and if it does happen, we can treat and reverse it.

Blood draw: You may feel some pain at the needle entry site. There is a slight risk of bleeding around the site. This is not dangerous, but it could cause a bruise. Some people feel lightheaded or dizzy after having blood drawn. To reduce your risk of falling, we will monitor you closely and ask you about these symptoms before we allow you to stand up.

Microbiome sampling by swab method: This may cause minor discomfort to you.

Questionnaire: You may feel uncomfortable answering some of the questions about your personal information and health information. You can choose not to answer questions that make you feel uncomfortable.

Psychosocial risks: We do not anticipate psychological harm to you during the study. If you have any psychological concerns from the questions asked or during sampling, please let us know.

Risks from Biopsy
The biopsy may cause pain and discomfort. It is possible, but not likely, that it can become infected. In very rare cases, people might have an allergic reaction to the numbing medicine. Allergic reactions are characterized by skin rash lesions, urticaria, and edema or anaphylactoid reactions (rash/hive, flushing of the face, itching, wheezing and tightness in the throat). Allergic reactions may occur as a result of sensitivity either to local anesthetic agents or to the methylparaben used as a preservative in the multiple dose vials. There may be a small scar from the biopsy.

Confidentiality
We will keep your information confidential, however, a risk of taking part in this study is that your confidential information might be shared accidentally with someone who is not on the study team and is not supposed to see or know about your information. This is very unlikely, because the study team takes confidentiality of your information seriously. Your research records will be kept confidential and your name will not be used in any written or verbal reports. Your information will be given a code number and separated from your name or any other information that could identify you. The form that links your name to the code number will be kept in a locked file cabinet and only the investigator and study staff will have access to the file. All information will be kept in a secure manner and computer records will be password protected. Your study and specimens will be kept as long as they are useful for this research.

The only people who can see your research records are:

- the research team and staff who work with them
- clinicians and staff at Montefiore who review your records for your care
- FDA, who is funding this research
- Groups that review research (the Einstein IRB, and the Office for Human Research Protections)

These people, who receive your health information, may not be required by privacy laws to protect it and may share your information with others without your permission, if permitted by laws governing them. All of these groups have been asked to keep your information confidential.

Are there any times you would not keep my data confidential?

If you give us information that suggests that your child or any other child is being abused, we are required by law to report that information to the Administration for Children's Services (ACS). Reporting this information may put you, your family, or others who are involved at risk of questioning and legal action by the authorities.

If you give us information that you may hurt yourself or someone else we might have to inform the concerning authorities.

When results of an FDA research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the FDA will not release any information about your research involvement without your written permission. *However, if you sign a release of information form, for example, for an insurance company, Montefiore will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.*

The Federal Privacy Act protects the confidentiality of your Montefiore medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

Certificate of Confidentiality

As a way to protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health, which is funding this study. If information from this study was requested or subpoenaed by government agencies or the courts, we will use the Certificate to attempt to legally refuse to provide it. This is rare – in only a few cases did researchers have to use the Certificate, and it was honored most of the time, but not every time. There are several kinds of situations that the Certificate does not apply. For example, we are still required to report child abuse and some diseases, and we must make data available to the government for a review or evaluation of our research. The Certificate does not prevent you or a member of your family from voluntarily sharing information. Similarly, if an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information

Genetic Testing

Genes are made up of DNA, and have the information needed to build and operate the human body. Your blood or tissue will be tested for genetic changes that may relate *to* **an increase or decrease in the chance of developing Sickle cell Ulcer.** The information obtained from these tests will include genetic information about you. To protect your identity, we will give your specimen(s) a code number. Genetic factors are inherited and run in families. Since genetic information is shared by family members, the information from these tests may apply to your family members, as well.

If there is a positive test result, you may want to have additional independent testing and consult with a genetic counselor. Genetic counseling is not provided through the study. The Genetic Information Nondiscrimination Act (GINA) may protect you from health insurance or employment discrimination based on genetic information. The law says that health insurance companies and group health plans may not ask for genetic information from this research and may not use genetic information when making decision about eligibility or premiums

The law will not stop health insurance companies from using genetic information to decide whether to pay claims. The law will not help you get other types of insurance (such as: life, disability or long-term care) and these insurance companies sometimes use information from genetic testing to deny life insurance or disability coverage to applicants.

The meaning of the results of this genetic research is not known; therefore we will not give you the results of these studies. You should be aware that insurance companies sometimes use information from genetic testing to deny life insurance or disability coverage to applicants. If you decide to participate in this research study, if your insurance company asks, you should state that although you have had a genetic test performed as part of a research study, the test is investigational and has no clinical meaning, and you will not be provided with the results.

Specimen Banking (Future Use and Storage)

We will store your specimens and information about you in a “bio bank”, which is a library of information and specimens (tissue and blood) from many studies. These specimens and information can be linked to you. In

the future, researchers can apply for permission to use the specimens and information for new studies to prevent, diagnose or treat disease, including genetic research. Some of your de-identified genetic and health information (not linked to you) may be placed into one or more scientific databases. These may include databases maintained by the federal government. Your specimens and information may be kept for a long time, perhaps longer than 50 years. You may remove your consent for future research at any time by contacting the Principal Investigator named on the first page of the consent or the IRB office at 718-430-2237. If you do, we will destroy remaining specimens and information but if these were already shared with other researchers, we cannot get them back.

Some researchers may develop tests, treatments or products that are worth money. You will not receive payment of any kind for your specimens and information or for any tests, treatments, products or other things of value that may result from the research.

INITIAL ONE (1) OF THE FOLLOWING OPTIONS

_____ I consent to have my information used for future research studies.

_____I do NOT consent to have my information used for future research studies. Information about me will be kept as long as required by regulations and institutional policy, but will not be used for future studies.

Will I receive payment for being in the study?

We will give you $20 to help cover the costs of transportation to the hospital. If you live outside of an 18-mile radius from the hospital, a higher compensation may be given. As follow-up visit 1 will take approximately 5 hours to complete we will provide $100 reimbursement for this visit. Individuals who agree to have the biopsy will receive an additional $100, one time only. You will be reimbursed by ClinCard at the beginning of each study visit. The card will be uploaded with the reimbursement amount within 2-3 days of each study visit. You can use the debit card like cash.

Your biological materials will be used only for research and will not be sold or used directly for the production of commercial products. The research done with your biological materials may help to develop new products in the future; however you will not receive payment as a result of your participation.

Will it cost me anything to participate in this study?

There will be no cost to you to participate in the study.

What will happen if I am injured because I took part in this study?

If you are injured as a result of this research, only immediate, essential, short term medical treatment, as determined by the participating hospital or sponsoring company will be available for the injury without charge to you personally.

- No monetary compensation will be offered.
- You are not waiving any of your legal rights by signing this informed consent document
- If additional treatment is required as a result of a physical injury related to the research, necessary medical treatment will be provided to you and billed to your insurance company or to you as part of your medical expenses.

Immediately report any discomforts, problems or injuries you experience during the course of your participation in the study to Dr. Caterina Minniti at (718) 920-4137/4180.

What else do I have to do?

- You must tell the research study doctor about any past and present diseases or allergies you are aware of and about all medications you are taking including “over-the-counter” remedies and nutritional supplements or herbs and if there are any changes to your medicines.

- You may carry out all your normal daily activities.

Undesirable Interactions between Nitrate and other drugs

Methemoglobin levels can be elevated by the presence of other drugs. The following list of medications should be avoided while on study:

- Anesthetics (local): Benzocaine, procaine, prilocaine, Anbesol, Orajel
- Antimalarials: chloroquine, primaquine, quinacrine
- Aniline dyes
- Chlorates Dapsone
- Diarylsulfonylureas
- Doxorubicin
- Metoclopramide
- Nitric and nitrous oxide
- Nitrobenzenes (shoe and floor polish and in paints solvents)
- Nitroethane (artificial nail remover, propellant, fuel additive
- Nitrofurantoin (furadantin)
- Pyridium (phenazopyridine)
- Phenacetin
- Phenylhydrazine
- Rasburicase
- Sulfonamides (sulfacetamide, sulfamethoxazole, sulfanilamide, sulfapyridine)

Therefore, it is very important that you tell your study doctor about all of the medications and treatments you are receiving before the study and any new drug before you starting taking it during the course of the study. This includes “over the counter” medications, herbal and natural remedies, and vitamins in addition to prescription medications. Your study doctor will let you know if your medications can be taken with Nitrate.

We may re-contact you

In the future, we may want to obtain additional samples or follow-up information about your health or medical care. Also, if there is a new study on Sickle Cell Disease that you may be eligible for, we would like your consent to re-contact you. If you move, please contact us with your new address, email and telephone number so we can contact you for any follow-up or to invite you to participate in additional research on sickle cell disease. Additionally, we encourage you to contact us if you have questions about the progress of this study.

INITIAL YOUR CHOICE BELOW
I consent to be contacted in the future to learn about:
_____ New research protocols that I may wish to join.
_____ General information about research findings.

Are there possible benefits to me?

The possible benefits of taking part in this study include that your ulcer may decrease in size and be less painful.

What choices do I have other than participating in this study?

You can refuse to participate in the study. If you decide not to participate, the medical care providers at this facility will still give you all of the standard care and treatment that is appropriate for you.

What if I change my mind?

You may choose to withdraw from this study at any time. This will not affect your care and you will

continue to be treated at this facility. However, your data, biological materials, and survey responses that have already been collected will not be discarded or removed; they will be kept and included in the study.

Who else will know that I am in this study?

Your data/biological materials that we collect from you will be maintained by the researchers at Montefiore and may be shared with other researchers in the future, but only after your name and all identifying information have been removed. Data from this study will be identified with a code number instead of your name. The key for this code will be stored in a password-protected file by the Principal Investigator.

Your samples will be stored indefinitely in a secured freezer and will be sent for genetic testing. Your blood sample and medical information will be labeled with a code and not your name. Only Dr. Caterina Minniti; Dr. Gregory Kato, MD; Dr. Giacomo Vinces, MD; Dr. Ugochi Ogu, MD; and study associate investigators will have the information that matches the code to your personally identifiable information. Access to the code under the direction of the Principal Investigator will be restricted.

Your coded blood (or other tissue) samples will be sent to an approved sequencing laboratory for detailed analysis. Remaining portions of your samples will be stored for an unlimited period of time for future use in research related to diseases or, perhaps, in other research projects. Information from analyses of your coded samples and your coded medical information will be put into Montefiore databases along with information from the other research participants. These databases will be accessible by the Internet. Additionally, once your samples have been analyzed and the information deposited into the database, your data cannot be withdrawn.

Your coded medical information and information from more detailed analyses of your coded samples will be put in a controlled-access database. Controlled-access data can only be obtained if a qualified researcher has been authorized by the appropriate Data Access Committee.

The information in this Controlled-access database will be available only to researchers requesting access to conduct research on sickle cell disease and/or sickle cell disease leg ulcers.

CONSENT TO PARTICIPATE

I have read the consent form and I understand that it is up to me whether or not I participate. I know enough about the purpose, methods, risks and benefits of the research study to decide that I want to take part in it.
I understand that I am not waiving any of my legal rights by signing this informed consent document.
I will be given a signed copy of this consent form.

Printed name of participant	Signature of participant	Date	Time

Printed name of the person conducting the consent process		Date	Time