Informed Consent Cover Page for FDAAA consent posting:

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PRINCIPAL INVESTIGATOR: Arun Shet, M.D.

STUDY TITLE: Venous Thrombosis Biomarkers in Sickle Cell Disease and Sickle Cell Trait

STUDY SITE: National Heart, Lung and Blood Institute

Cohort: Affected (SCD & SCT) and healthy subjects

Consent Version: 06-22-2023

WHO DO YOU CONTACT ABOUT THIS STUDY?

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KEY INFORMATION ABOUT THIS RESEARCH

This consent form describes a research study and is designed to help you decide if you would like to be a part of the research study.

You are being asked to take part in a research study at the National Institutes of Health (NIH). This section provides the information we believe is most helpful and important to you in making your decision about participating in this study. Additional information that may help you make a decision can be found in other sections of the document. Taking part in research at the NIH is your choice.

The purpose of this research is to study blood clotting in Sickle Cell Disease (SCD) because it is the most common cause of vascular death after a heart attack or stroke. Abnormal clotting of blood in a deep vein of your upper or lower limbs is called a deep vein thrombosis. When this clot travels towards and blocks a blood vessel in the lung, it is called a pulmonary embolism. Some but not all SCD patients appear to be a greater risk for developing deep vein thrombosis and pulmonary embolism.

In this study, we will look at the blood of SCD patients who have venous thromboembolism (VTE) and look for specific changes in their blood. For patients with SCD, we may collect blood samples during an acute pain attack and in between pain attacks. For all patients including healthy volunteers, we may collect blood samples if you experience a venous blood clot. Your blood will be used to study blood markers which may help to identify SCD patients that are at a higher risk for blood clotting and help target them for treatment to prevent blood clots. You will not receive experimental treatment under this protocol.

You are invited to take part in this study because you have one of the following: sickle cell disease; the trait for SCD (SCT); healthy volunteer. You may also be followed on other NHLBI protocols. You may also have a previous history of a blood clot (deep vein thrombosis and/or

pulmonary embolism). If you are eligible for the study, you will be placed in one of the four groups/cohorts below.

Cohorts	Description
Cohort 1a **SCD + VTE (cases)**	50 men and women with SCD and at least one VTE within the past 5 years.
Cohort 1b **SCD only (controls)**	50 men and women with SCD that do not have a history of VTE
Cohort 2a **SCT (cases)**	50 men and women with SCT
Cohort 2b **Ethnic matched, no SCT (controls)**	50 ethnically matched men and women with no history or laboratory evidence for SCD, SCT or VTE

Your participation in this study will last approximately 2 years. An initial visit will involve review of past medical history, a physical examination and a blood sample which are part of the research study.

Cohort 1 patients will have the following:

- Baseline clinical evaluation during enrollment and collection of blood samples. Cohort 1 will be invited to the Clinical Center for a follow up visit 2 years after the baseline visit for clinical evaluation, blood samples and then taken off study.
- Follow up phone calls every 3 months (+/- 30 days) until Month 21 to obtain clinical information on acute events and monitor their health status related to SCD and VTE recurrence. Depending on the occurrence of these events, participants will be invited to the Clinical Center for blood studies.
- If you experience a blood clot, you may be invited to come back to NIH for additional blood tests.
- For SCD patients, if you experience a pain crisis, you may be invited to come back around the time of the pain crisis for additional blood tests.
- During the study, we may ask for medical records from outside hospitals and clinics to help gather information about your medical conditions.

Cohort 2 patients will have:

- Baseline clinical evaluation during enrollment and collection of blood samples.

Will have 1 annual follow up phone call for 2 years to obtain information on the development of VTE.

The general risks associated with this study pertain to the following: blood draw and genetic testing. The risks associated with the blood draws are minimal and involve pain at the site of blood withdrawal, mild bruising at the site and potential for local infection at the site. The risks associated with doing genetic testing of blood pertain to the results that may be obtained from the genetic test, which is described below.

You will be offered compensation for your time and inconvenience for participation and completion of the research study. In addition, reimbursement for travel will be provided under this protocol.

You can discuss with your doctor to see if there are other alternative studies that you can participate in if you decide not to participate in this one.

There is no immediate benefit to you by taking part in this study, but it could help others in the future.

The remaining document will now describe more about the research study. This information should be considered before you make your choice. Members of the study team will talk with you about the information described in this document. Some people have personal, religious, or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). Take the time needed to ask any questions and discuss this study with NIH staff, and with your family, friends, and personal health care providers.

If the individual being asked to participate in this research study is not able to give consent for themselves, you, as the Legally Authorized Representative, will be their decision-maker and you are being asked to give permission for this person to be in this study. For the remainder of this document, the term "you" refers to you as the decision-maker and/or the individual being asked to participate in this research.

IT IS YOUR CHOICE TO TAKE PART IN THE STUDY

You may choose not to take part in this study for any reason. If you join this study, you may change your mind and stop participating in the study at any time and for any reason. In either case, you will not lose any benefits to which you are otherwise entitled. However, to be seen at the NIH, you must be taking part in a study or are being considered for a study. If you do choose to leave the study, please inform your study team to ensure a safe withdrawal from the research.

WHY IS THIS STUDY BEING DONE?

You are invited to take part in this study because you identify as belonging to one of the following categories: sickle cell disease, the trait for SCD (SCT) or healthy individuals. You may also have a previous history of a blood clot (deep vein thrombosis and/or pulmonary embolism). The purpose of this research is to study blood clotting in SCD because it is the most common cause of vascular death after a heart attack or stroke. Abnormal clotting of blood in a deep vein of your upper or lower limbs is called a deep vein thrombosis. When this clot travels towards and blocks a blood vessel in the lung, it is called a pulmonary embolism. Some but not all SCD patients appear to be

a greater risk for developing deep vein thrombosis and pulmonary embolism. In this study, we will examine the blood of SCD patients who develop VTE and look for specific changes in the levels of a clotting protein. If you have SCD, we may study blood samples collected during an acute pain attack and in between attacks and when you experience a deep venous blood clot. Your blood will be used to study blood markers indicative of the risk of developing a blood clot. This could help identify SCD patients that are at a higher risk for blood clotting and targeting them for treatment to prevent blood clots. You will not receive experimental treatment under this protocol.

WHAT WILL HAPPEN DURING THE STUDY?

A member of the study team will tell you about the study and ask you some questions to determine if you are eligible for this study. If you decide to take part in this study, you will be asked to sign this consent form after you have read it and understood it.

After signing the consent, we will do the following on your 1st visit:

- Take down your medical history (will ask about your past health condition)
- Perform a physical examination (like taking your vital signs and checking the general health of your body)
- Review your medical records
- Take a blood sample for research
- As part of this study, we will test you for infection with the human immunodeficiency virus (HIV), the virus that causes AIDS. If you are infected with HIV you may still be able to participate in this study depending on your treatment and blood counts. We will tell you what the results mean, how to find care, how to avoid infecting others, how we report HIV infection, and the importance of informing your partners at possible risk because of your HIV infection.
- We are requesting your permission to perform genome/exome sequencing on your blood samples and link this to your medical and/or family history. Your blood and tissue samples contain genes, which are made up of DNA (deoxyribonucleic acid) which serves as the "instruction book" for the cells that make up our bodies. We will test your DNA for genes that can contribute to clotting in SCD. Gene sequencing will determine the exact order of the base pairs (chemical letters) in your blood cells. Your sample, when correlated with blood clotting events will help us study how genes influence clotting in SCD. Because we don't know much about how these genes can affect sickle cell disease, the results of our research studies will not be provided to you or your referring doctor.

A visit at the NIH may be offered to you approximately 2 - 4 weeks after the initial visit to discuss the results of clinical blood tests.

For all Follow Up Visits at the NIH we will:

- Review your medical history
- Perform a physical examination
- If needed, review and obtain any outside medical records
- May take additional blood sample for research

Follow Up by phone:

- Review your medical history
- If needed, review and obtain any outside medical records
- Review any current medications you are taking

If you have a blood clot or a pain crisis while participating in the study, you may be invited to return to the NIH clinical center for the following:

- Review your medical history
- Perform a physical examination
- If needed, review and obtain any outside medical records
- Review any current medications you are taking
- May take additional blood sample for research

The table below shows the amount of blood that will be taken for cohorts 1 and 2 throughout the research study:

Cohort 1 & 2 patients	Cohort 1 patients only		
Baseline	End of Study Month 24	VTE Visit	Pain Crisis Visit
~60ml	~45 mL	~30 to 60ml	~60ml

HOW LONG WILL THE STUDY TAKE?

If you agree to take part in this study, your involvement is expected to last for about 2 years.

After your first initial visit, you may have multiple visits depending upon how many VTE or pain crisis episodes you may have. These additional study visits may last up to 4 hours.

You will also have phone follow ups which may involve a request for additional medical records. The phone calls may last up to 30 minutes in length.

HOW MANY PEOPLE WILL PARTICIPATE IN THIS STUDY?

We plan to have approximately 200 people participate in this study at the NIH. Fifty men and women with sickle cell disease with history of blood clot. Fifty men and women with sickle cell disease with no history of blood clot. Fifty men and women with sickle cell trait. Fifty healthy men and women without sickle cell disease, sickle cell trait, or history of blood clot.

WHAT ARE THE RISKS AND DISCOMFORTS OF BEING IN THE STUDY?

a) Blood collection:

There may be some discomfort on your arm when we collect your blood with a needle. There is a small chance that you will get a bruise, feel lightheaded, faint, or have an infection at the place where you were pricked.

b) Genetic and DNA analysis:

Issues related to your confidentiality: Some people are concerned that information about them from their medical records could be given out without them knowing about it. Possible problems might include insurance or employment discrimination. Steps to protect your information are detailed below. These problems may also occur if you give out information yourself or agree to have your research records given out. Information from this study will be identified with a code number instead of your name. The key for this code will be stored in a locked file cabinet.

Protections against misuse of genetic information

This study involves genetic testing on samples. Some genetic information can help predict future health problems of you and your family and this information might be of interest to your employers or insurers. The Genetic Information Nondiscrimination Act (GINA) is a federal law that prohibits plans and health insurers from requesting genetic information or using genetic information. It also prohibits employment discrimination based on your health information. However, GINA does not address discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. GINA also does not protect you against discrimination based on an already-diagnosed condition or disease that has a genetic component.

We may publish results of this research study in scientific journals and public databases, including your medical history and other medical information but the information provided in the publications will be anonymous. It is possible but unlikely that you and/or a family member could be identified because of such publications.

Researchers who will have access to genetic information about you will take measures to maintain the confidentiality of your genetic information.

Risks Related to this Study:

Psychological or Social Risks Associated with Return of Incidental or Secondary Findings

As part of the research study, it is possible that you could learn that you have genetic risks for another disease or disability. This may be upsetting and, depending on what you learn, might create a need to make challenging decisions about how to respond.

Although your genomic information is unique to you, you share some genomic similarities with your children, parents, brothers, sisters, and other blood relatives. Therefore, learning your research results could mean something about your family members and might cause you or your family distress. Before joining the study, it may be beneficial to talk with your family members about whether and how they want you to share your results with them.

Privacy Risks Associated with Return of Incidental or Secondary Findings

Although your genetic information is unique to you, you do share some genetic information with your children, parents, brothers, sisters, and other blood relatives. Consequently, it may be possible that genetic information from them could be used to help identify you. Similarly, it may be possible that genetic information from you could be used to help identify them. Patterns of genetic variation also can be used by law enforcement agencies to identify a person or his/her blood relatives.

What are the risks related to pregnancy?

There are no risks related to pregnancy. However, because pregnancy changes the blood markers we are looking for, we cannot collect information for this study while you are pregnant. If you do become pregnant during the study period, you are requested to notify us.

WHAT ARE THE BENEFITS OF BEING IN THE STUDY?

You will not benefit from being in this study.

Are there any potential benefits to others that might result from the study?

In the future, other people might benefit from this study because the study may find a marker that could possibly identify those SCD patients who have a higher risk for developing a blood clot. This would identify who should be treated with a blood thinner. It could also help determine how long treatment with the blood thinner should continue and when it should be stopped.

WHAT OTHER OPTIONS ARE THERE FOR YOU?

You do not have to participate in this study if you do not want to. You may withdraw from this study at any time. If you decide to withdraw from the study, we would like to keep your test results to properly analyze this research study. If you have concerns about this, please speak with members of your research team.

If you decide not to participate in this research study, other treatments or medications may be available for the treatment of SCD. There may also be other clinical research studies in which

you may choose to participate. You may discuss these alternatives with your doctor and decide whether to participate in this study.

DISCUSSION OF FINDINGS

New information about the study

If we find out any new information that may affect your choice to participate in this study, we will get in touch with you to explain what we have learned. This may be information we have learned while doing this study here at the NIH or information we have learned from other scientists doing similar research in other places.

Return of research results

You will be provided with the results of the standard clinical labs, but the results of our research studies will not be provided to you or your referring doctor.

EARLY WITHDRAWAL FROM THE STUDY

Discontinuing Participation:

- If you decide to stop participating in this study, you may request this by either informing the investigators or by writing to the research team to the address at the end of this consent (under Problems and Questions on last page of consent). You will not be asked for further information or samples.
- If we are unable to contact you or reach you.
- If you become pregnant.
- When the study has completed.

STORAGE, SHARING AND FUTURE RESEARCH USING YOUR SPECIMENS AND DATA

Will your specimens or data be saved for use in other research studies?

As part of this study, we are obtaining specimens and data from you. We will remove all the identifiers, such as your name, date of birth, address, or medical record number and label your specimens and data with a code so that you cannot easily be identified. However, the code will be linked through a key to information that can identify you. We plan to store and use these specimens and data for studies other than the ones described in this consent form that are going on right now, as well as studies that may be conducted in the future. These studies may provide additional information that will be helpful in understanding sickle cell disease, or other diseases or conditions. This could include studies to develop other research tests, treatments, drugs, or devices, that may lead to the development of a commercial product by the NIH and/or its research or commercial partners. There are no plans to provide financial compensation to you if this happens. Also, it is unlikely that we will learn anything from these studies that may directly benefit you.

I give permission for my coded specimens and data to be stored and used for future research as described above.

_____ Yes _____ No

Initials Initials

Will your specimens or data be shared for use in other research studies?

We may share your coded specimens and data with other researchers. If we do, while we will maintain the code key, we will not share it, so the other researchers will not be able to identify you. They may be doing research in areas similar to this research or in other unrelated areas. These researchers may be at NIH, other research centers and institutions, or commercial entities.

I give permission for my coded specimens and data to be shared with other researchers and used by these researchers for future research as described above.

_____ Yes _____ No

Initials Initials

If you change your mind and do not want us to store and use your specimens and data for future research, you should contact the research team member identified at the top of this document. We will do our best to comply with your request but cannot guarantee that we will always be able to destroy your specimens and data. For example, if some research with your specimens and data has already been completed, the information from that research may still be used. Also, for example, if the specimens and data have been shared already with other researchers, it might not be possible to withdraw them.

In addition to the planned use and sharing described above, we might remove all identifiers and codes from your specimens and data and use or share them with other researchers for future research at the NIH or other places. When we or the other researchers access your anonymized data, there will be no way to link the specimens or data back to you. We will not contact you to ask your permission or otherwise inform you before we do this. We might do this even if you answered "no" to the above questions. If we do this, we would not be able to remove your specimens or data to prevent their use in future research studies, even if you asked, because we will not be able to tell which are your specimens or data.

NIH policies require that your clinical and other study data be placed in an internal NIH database that is accessible to other NIH researchers for future research. Usually, these researchers will not have access to any of your identifiers, such as your name, date of birth, address, or medical record number; and your data will be labeled with only a code. We cannot offer you a choice of whether your data to be placed in this database or not. If you do not wish to have your data placed in this database, you should not enroll in this study.

How long will your specimens and data be stored by the NIH?

Your specimens and data may be stored by the NIH indefinitely.

Risks of storage and sharing of specimens and data

When we store your specimens and data, we take precautions to protect your information from others that should not have access to it. When we share your specimens and data, we will do everything we can to protect your identity, for example, when appropriate, we remove information

that can identify you. Even with the safeguards we put in place, we cannot guarantee that your identity will never become known or someone may gain unauthorized access to your information. New methods may be created in the future that could make it possible to re-identify your specimens and data.

COMPENSATION, REIMBURSEMENT, AND PAYMENT

Will you receive compensation for participation in the study?

Some NIH Clinical Center studies offer compensation for participation in research. The amount of compensation, if any, is guided by NIH policies and guidelines.

You will be offered compensation for your time and inconvenience for participation and completion of the research study. In addition, reimbursement for travel will be provided under this protocol.

Upon completion of the research study, you may be compensated based on the table below. Additional compensation may be given to those patients who return for additional research samples at time of an acute pain attach and VTE.

Compensation for Cohort 1

Procedure(s)/Test(s)	**$/visit**	**Frequency**	**Total $$**
Physical Exam (multiple visits may increase compensation)	$25	2	$50
Blood Draw (multiple visits may increase compensation)	$50	2	$100
Phone Questionnaire	$10	1 per phone call x 7	$70
OUTPATIENT- **1st HOUR**	$20 for 1st hour	2 visits to occur	$40
OUTPATIENT TIME- **Not to Exceed More than 4 Hours**	$10/hour	4 hours/visits x 2	$80
TOTAL $$$			**$340**

Compensation for Cohort 2

Procedure(s)/Test(s)	**$**	**Frequency**	**Total $$**
Physical Exam (multiple visits may increase compensation)	$25	1	$25
Blood Draw (multiple visits may increase compensation)	$50	1	$50
Phone Questionnaire	$10/phone call	1 per phone call x 2	$20
OUTPATIENT- **1st HOUR**	$20 for 1st hour	1 visit to occur	**$20**
OUTPATIENT TIME- **Not to Exceed More than 4 Hours**	$10/hour	4 hours/visits	$40
TOTAL $$$			**$155**

If you are unable to finish the study, you will receive for the parts you completed.

With few exceptions, study compensation is considered taxable income that is reportable to the Internal Revenue Service (IRS). A "Form 1099-Other Income" will be sent to you if your total payments for research participation are $600 or more in a calendar year. If you have unpaid debt to the federal government, please be aware that some or all of your compensation may be automatically reduced to repay that debt on your behalf.

Will you receive reimbursement or direct payment by NIH as part of your participation?

Some NIH Clinical Center studies offer reimbursement or payment for travel, lodging or meals while participating in the research. Local taxi travel mileage reimbursement will be provided as needed.

Will taking part in this research study cost you anything?

NIH does not bill health insurance companies or participants for any research or related clinical care that you receive at the NIH Clinical Center.

- You will receive study care at no charge to you. This may include surgery, medicines, laboratory testing, x-rays or scans done at the Clinical Center, National Institutes of Health (NIH), or arranged for you by the research team to be done outside the Clinical Center, NIH if the study related treatment is not available at the NIH.
- There are limited funds available to cover the cost of some tests and procedures performed outside the Clinical Center, NIH. You may have to pay for these costs if they are not covered by your insurance company.
- Once you have completed taking part in the study, medical care will no longer be provided by the Clinical Center, NIH.

CLINICAL TRIAL REGISTRATION AND RESULTS REPORTING

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

CONFIDENTIALITY PROTECTIONS PROVIDED IN THIS STUDY

Will your medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The NHLBI and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Institutes of Health Intramural Institutional Review Board

The researchers conducting this study and the NIH follow applicable laws and policies to keep your identifying information private to the extent possible. However, there is always a chance that, despite our best efforts, your identity and/or information about your participation in this research may be inadvertently released or improperly accessed by unauthorized persons.

In most cases, the NIH will not release any identifiable information collected about you without your written permission. However, your information may be shared as described in the section of this document on sharing of specimens and data, and as further outlined in the following sections.

Further, the information collected for this study is protected by NIH under a Certificate of Confidentiality and the Privacy Act.

Certificate of Confidentiality

To help us protect your privacy, the NIH Intramural Program has received a Certificate of Confidentiality (Certificate). With this certificate, researchers may not release or use data or information about you except in certain circumstances.

NIH researchers must not share information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if requested by a court.

The Certificate does not protect your information when it:

1. is disclosed to people connected with the research, for example, information may be used for auditing or program evaluation internally by the NIH; or
2. is required to be disclosed by Federal, State, or local laws, for example, when information must be disclosed to meet the legal requirements of the federal Food and Drug Administration (FDA);
3. is for other research;
4. is disclosed with your consent.

The Certificate does not prevent you from voluntarily releasing information about yourself or your involvement in this research.

The Certificate will not be used to prevent disclosure to state or local authorities of harm to self or others including, for example, child abuse and neglect, and by signing below you consent to those disclosures. Other permissions for release may be made by signing NIH forms, such as the Notice and Acknowledgement of Information Practices consent.

Privacy Act

The Federal Privacy Act generally protects the confidentiality of your NIH medical information that we collect under the authority of the Public Health Service Act. In some cases, the Privacy Act protections differ from the Certificate of Confidentiality. For example, sometimes the Privacy Act allows release of information from your record without your permission, for example, if it is requested by Congress. Information may also be released for certain research purposes with due consideration and protection, to those engaged by the agency for research purposes, to certain federal and state agencies, for HIV partner notification, for infectious disease or abuse or neglect reporting, to tumor registries, for quality assessment and medical audits, or when the NIH is involved in a lawsuit. However, NIH will only release information from your medical record if it is permitted by both the Certificate of Confidentiality and the Privacy Act.

POLICY REGARDING RESEARCH-RELATED INJURIES

The NIH Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the NIH, the NIH Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

PROBLEMS OR QUESTIONS

If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Arun Shet, M.D., Telephone: 301-827-6808 email : arun.shet@nih.gov. Other researchers you may call are: Dianna Lovins, RN at Telephone: 240-552-0245. You may also call the NIH Clinical Center Patient Representative at 301-496-2626, or the NIH Office of IRB Operations at 301-402-3713, if you have a research-related complaint or concern.

CONSENT DOCUMENT

Please keep a copy of this document in case you want to read it again.

Adult Research Participant: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I consent to participate in this study.

Signature of Research Participant	Print Name of Research Participant	Date

Legally Authorized Representative (LAR) for an Adult Unable to Consent: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I am legally authorized to make research decisions on behalf of the adult participant unable to consent and have the authority to provide consent to this study. As applicable, the information in the above consent was described to the adult participant unable to consent who agrees to participate in the study.

Signature of LAR	Print Name of LAR	Date

Investigator:

Signature of Investigator	Print Name of Investigator	Date