Informed Consent Form

Kinetics of Donor Red Blood Cell Survival in Sickle Cell Disease

IRB Approval Date: April 16, 2024

NCT04426591

You Are Being Asked to Be in a Research Study

You are being asked to be in a research study. A research study is designed to answer a scientific question. If you agree to be in the study you will be one of 40 people who are being studied at Emory, Children's Healthcare of Atlanta and Grady Health System.

Why is this study being done?
This study is being done to answer the question: When a person with sickle cell disease or thalassemia receives a red blood cell transfusion, why does the transfusion last for a longer time in some people than in others? You are being asked to be in this research study because you have sickle cell disease or thalassemia and receive monthly blood transfusions (chronic transfusion therapy).

Do you have to be in the study?
It is your decision to be part of this research study. You do not have to be in it. Your choice will not affect your access to medical care for your condition. Before you make your decision, you should take time to learn about the study.

What do I have to do if I choose to participate in this study?
If you are eligible and want to be part of the study, you will participate for 18 study visits. The researchers will ask you to do the following: Receive your scheduled blood transfusion which will have biotin (vitamin B7) added to the red blood cells in order to measure them. You will then be asked to come the next day for a blood sample, then once a week for 12 weeks for blood samples, then once a month for 6 months. You will also have an ultrasound to measure the size of your spleen at the start of the study. You will be given the option of doing additional weekly blood draws from weeks 13 to 16, to continue to measure the survival of your blood transfusion. It is also possible you will be given the option to do another transfusion of biotin-labeled red blood cells in the future.

How is this study going to help you?
If you are in the study, you will be helping the researchers answer the study question. The information learned may help to guide management of your chronic transfusion therapy.

What are the risks or discomforts I should know about before making a decision?
The study will take time. All studies have some risks. Some risks are relatively small, like being bored or losing time. Some are more serious – for this study, these include a blood transfusion reaction including forming antibodies against the biotin-labeled red blood cells, loss of privacy, and breach of confidentiality. A full list of expected risks, their frequency and severity are in the "What are the possible risks and discomforts?" section of this document.

Alternatives to Joining This Study
Since this is not a treatment study, the alternative is not to participate.

Costs
You WILL NOT have to pay for any of the study procedures, in particular those that are not covered by your medical insurance.

The study team can help you work out how much you might have to pay. There is more information in the cost section below.

What Should I Do Next?
Read this form, or have it read to you. Make sure the study doctor or study staff explains the study to you. Ask questions (e.g., about exact time commitment, about unfamiliar words, more details on specific procedures, etc.) Make sure you understand which parts of the are research and which are standard care that you would have even if you did not join the study. Take time to consider this, and talk about it with your family and friends.

Emory University, Children's Healthcare of Atlanta and
Children's Healthcare of Atlanta at Hughes Spalding Hospital
Grady Health System
Consent to be a Research Subject / HIPAA Authorization

Title: Kinetics of Donor Red Blood Cell Survival in Sickle Cell Disease

Principal Investigator-Sponsor: Marianne Yee, MD

Supporter: National Heart, Lung and Blood Institute (NHLBI) / National Institutes of Health (NIH)

If you are the legal guardian of a child who is being asked to participate, the term "you" used in this consent refers to your child

Introduction
You are being asked to be in a medical research study. This form is designed to tell you everything you need to think about before you decide if you want to be a part of the study. **It is entirely your choice. If you decide to take part, you can change your mind later on and withdraw from the research study.** The decision to join or not join the research study will not cause you to lose any medical benefits. If you decide not to take part in this study, your doctor will continue to treat you.

Before making your decision:
- Please carefully read this form or have it read to you
- Please listen to the study doctor or study staff explain the study to you
- Please ask questions about anything that is not clear

You can take a copy of this consent form, to keep. Feel free to take your time thinking about whether you would like to participate. You may wish to discuss your decision with family or friends. Do not sign this consent form unless you have had a chance to ask questions and get answers that make sense to you. By signing this form you will not give up any legal rights.

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.

What is the purpose of this study?
The Emory University Center for Transfusion and Cellular Therapies (CTCT) studies various aspects of blood transfusions. The purpose of this research is to study how transfused red blood cells survive in the circulation of a person with sickle cell disease or transfusion-dependent thalassemia, and how that survival may be different in different people or different blood units.

In this study, we would like to measure how long a red blood cell (RBC) transfusion survives in your circulation. We will do this at a time when you normally would be receiving a RBC transfusion for treatment of sickle cell disease or transfusion-dependent thalassemia. The blood units that you receive for 1 transfusion will have a small "label" added to them in the laboratory before transfusion. The label we will use is biotin, which is a naturally occurring vitamin that most people eat large amounts of every day. This type of labeling, which is for investigational purposes, has been used for

many years and has been shown to be very safe even when used in very young babies. This label allows us to measure the transfused RBC in your blood samples for weeks after the transfusion.

What will I be asked to do?

Before Transfusion: If you decided to participate in this study, we will take some of your blood that would otherwise be thrown away and use it for research tests. Before your transfusion, at the time of your regular pre-transfusion labs we will draw extra blood for research purposes (about 7-8mls or 1.5 teaspoons). You will also have an ultrasound of your abdomen to measure the size of your spleen.

Transfusion: You will come to clinic to receive one of your regular chronic transfusions, a small amount (20 mL) of the RBC in each unit will be labeled with biotin. This is the only transfusion with labeled blood you will receive.

After Transfusion: After the transfusion with labeled blood you will have your blood drawn at the following timepoints –

- Right after the transfusion is complete (about 5mls or 1 teaspoon)
- 24 Hours after the transfusion is complete (about 5mls or 1 teaspoon)
- Every week for 12 weeks (about 5mls or 1 teaspoon)
- Every month for 3 months (about 5mls or 1 teaspoon)

Whenever possible, we will do the blood sample at the same time that you are doing other routine blood work for your sickle cell or thalassemia health care. We anticipate that this will be about 10 extra blood draws beyond ones that you normally get for chronic transfusion therapy. If your routine blood banks tests shows that you have antibodies to RBC, the blood bank will follow regular procedures to match your future blood transfusions for those antibodies. Sometimes it is not clear if an antibody is aimed at transfused (donor) RBC or your own (self) RBC. If these antibodies are found, we will use a leftover sample of your blood to look at your detailed blood type for the protein (called an antigen) that the antibody may be targeting. Molecular testing of that blood type antigen may help to find out if the antibody is against the donor RBC or your own RBC. If we do this testing, we will tell you we are doing the test and the results.

If you still have biotin-labeled RBC detected in your blood samples by 12 weeks, you have the option to give a blood sample once a week (at week 13, week 14, week 15, and week 16) until 16 weeks after the transfusion. This would be up to 4 more blood draws than the original study. These blood samples would measure the presence of biotin-labeled RBC until they disappear. Each blood sample would be about 5 mls or 1 teaspoon.

After completion of the study visits, you may have the option to repeat another biotin-labeled transfusion and do the same blood draws again in the future. You might be invited to do this to learn more about blood transfusion survival at different time points. You might be invited to do this only if you had no adverse events that were related to the study after the first biotin-labeled transfusion. A repeat biotin-labeled transfusion is optional, and you do not have to consent to this to still participate in the study.

Who owns my study information and samples?

If you join this study, you will be donating your samples and study information. You will not receive any compensation if your samples or information are used to make a new product. If you withdraw from the study, data and samples that were already collected may be still be used for this study.

What are the possible risks and discomforts?

Risk of blood sampling: You will have a needle inserted into one of your veins to obtain blood samples. You may feel anxious. You may feel light-headed and you may faint. You may feel discomfort or pain. You may have bleeding from the puncture site. You may get a bruise, discoloration, redness or warmth at the puncture site.

Risk of transfusion with biotin labeled blood:
Many volunteers and patients in other centers have participated in a similar study, and they have not noted any adverse effects. The main risk is that you may develop an immune response to the biotin label on the transfused RBCs. We will be monitoring regularly for this response. There have not been any cases of people having adverse health effects from this immune response.

Blood transfusions are generally considered to be safe and are part of your regular sickle cell or thalassemia health care. Risks of blood transfusions include fever, skin rash or hives, allergy, and infection. We take a large number of precautions in the laboratory when we label the RBC transfusion with biotin, to minimize the chance of blood infection. This would be a very rare occurrence.

There may be side effects from the study or procedures that are not known at this time.

It is possible that the researchers will learn something new during the study about the risks of being in it. If this happens, they will tell you about it. Then you can decide if you want to continue to be in this study or not. You may be asked to sign a new consent form that includes the new information if you decide to stay in the study.

Will I benefit directly from the study?
This study is not designed to benefit you directly; however it is possible that the information learned may help to improve your future transfusion therapy. This study is designed to learn more about how RBCs survive in circulation, particularly in people who have sickle cell disease or thalassemia and receive blood transfusion as part of their health care. The study results may be used to help others in the future.

Will I be compensated for my time and effort?
You will receive $50 for each of the following visits: Pre Transfusion, Transfusion Day, and 24 hour Post Transfusion.
You will receive $35for each additional weekly or monthly visit to compensate you for your time and effort. If you do not finish the study, we will compensate you for the visits you have completed.
If you complete all study visits, you will receive $675 total, if you complete all required study visits.
If you choose to do the optional study visits at week 13, week 14, week 15, and week 16, you will also receive $35 for each of these visits. If you complete all 4 extra study visits, you will receive an additional $140. This would make the total compensation from the study up to $815, if you complete all study visits and all optional study visits.

If you consent to do a repeat biotin-labeled transfusion and blood draws again at a later time point, then you would receive the same compensation again for each visit, as detailed above.

Our preferred method of compensation will be the use of Clincards. All payments are made using a personal payment card. We issue this to you for free. The payment card is a prepaid debit card. It can be used exactly like a MasterCard. We load money onto your card electronically every time you need to be paid. The card scheme is run by Greenphire, an independent company specializing in payments for research studies and clinical trials. To issue your card, we need to give Greenphire some of your personal information. Banks and other financial institutions can access this information if they need to verify your identity when you use your card.

Emory University is required by law to report any payments we make to the IRS. To do this, Emory University Department of Finance needs to keep your Social Security Number on file. We are asking you to allow us to communicate your name, address, date of birth, research study name and Social Security Number to Greenphire and Emory University Department of Finance. If you want to receive e-mail or text alerts when payments are made to you, we will ask you to provide your e-mail or phone number as well. All of this information will be stored on computers

owned by Greenphire. Greenphire will not have access to any other information collected during this study. Full instructions about using your card are included when we issue it. Please ask if you have any questions or concerns about the card scheme.

We would also like the option of compensating you in the form of cash, check or gift card if ClinCard accessibility is not available. You will be asked to fill out a tax form, including your Social Security or Taxpayer Identification Number, in order to be reimbursed, depending on the amount and method of payment. Some payment methods involve mail coming to your house, which may be seen by others in your household. You can decline payment if you are concerned about confidentiality, or you can talk to the study team to see if there are other payment options. You will need to fill out a W-9 form.

In addition to the compensation you receive for your research study visits, transportation or reimbursement for gas used when driving your own car based on distanced traveled will be provided.

At each visit we will ask you how you arrived at the visit - A) drove personal car, b) public transportation, C) transportation service through the study.

If you would like to use the transportation service paid for by the study you need to let the study team know and they will arrange transportation for you.

If you drive your own car we will give you gift cards for gas based on the number of miles you drive to and from your house.

Round-trip driving distance	Gas card reimbursement
<25 miles	Provide one $25 card for every 6 visits
25 – 49 miles	Provide one $25 card for every 3 visits
50 – 99 miles	Provide one $25 card for every 2 visits
100 – 199 miles	Provide one $25 card for every 1 visit
200 – 299 miles	Provide two $25 cards for every 1 visit
≥300 miles	Provide three $25 cards for every 1 visit.

There will be no reimbursement offered if you choose to take public transportation.

What are my other options?

Participation in this study is voluntary. You do not have to participate in this study.

How will you protect my private information that you collect in this study?

Whenever possible, a study number, rather than your name, will be used on study records. Your name and other identifying information will not appear when we present or publish the study results.

Certificate of Confidentiality

There is a Certificate of Confidentiality from the National Institutes of Health for this Study. The Certificate of Confidentiality helps us to keep others from learning that you participated in this study. Emory and Children's Healthcare of Atlanta at Hughes Spalding will rely on the Certificate of Confidentiality to refuse to give out study information that identifies you. For example, if Emory or Children's Healthcare of Atlanta at Hughes Spalding received a subpoena for study records, it would not give out information that identifies you.

The Certificate of Confidentiality does not stop you or someone else, like a member of your family, from giving out information about your participation in this study. For example, if you let your insurance company know that you are in this study, and you agree to give the insurance company research information, then the investigator cannot use the Certificate to withhold this information. This means you and your family also need to protect your own privacy.

The Certificate does not stop Emory, Children's Healthcare of Atlanta, Children's Healthcare of Atlanta at Hughes Spalding and Grady Health System from making the following disclosures about you:

- Giving state public health officials information about certain infectious diseases,
- Giving law officials information about abuse of a child, elderly person or disabled person.
- Giving out information to prevent harm to you or others.

Giving the study sponsor or funders information about the study, including information for an audit or evaluation.

Storing and Sharing your Information

De-identified data from this study (data that has been stripped of all information that can identify you) may be placed into public databases where, in addition to having no direct identifiers, researchers will need to sign data use agreements before accessing the data. We will remove or code any personal information that could identify you before your information is shared. This will ensure that, by current scientific standards and known methods, it is extremely unlikely that anyone would be able to identify you from the information we share. Despite these measures, we cannot guarantee anonymity of your personal data.

Your data and specimens from this study may be useful for other research being done by investigators at Emory or elsewhere. To help further science, we may provide your deidentified data and/or specimens to other researchers. If we do, we will not include any information that could identify you. If your data or specimens are labeled with your study ID, we will not allow the other investigators to link that ID to your identifiable information.

In general, we will not give you any individual results from the study of the samples you give us. If we find something of urgent medical importance to you, we will inform you, although we expect that this will be a very rare occurrence.

Medical Record

If you have been an Emory, Children's Healthcare of Atlanta and Grady Health System patient before, then you already have a medical record with them. If you have never been an Emory, Children's Healthcare of Atlanta, Children's Healthcare of Atlanta at Hughes Spalding and Grady Health System patient, you do not have one. An Emory, Children's Healthcare of Atlanta, Grady Health System medical record will be made for you if an Emory, Children's Healthcare of Atlanta and Grady Health System provider or facility gives you any services or procedures for this study.

Copies of the consent form/HIPAA authorization that you sign will be put in any Emory, Children's Healthcare of Atlanta and Grady Health System medical record you have now or any time during the study.

Emory, Children's Healthcare of Atlanta and Grady Health System may create study information about you that can help with your care. For example, the results of study tests or procedures. These study results will be put in your Emory, Children's Healthcare of Atlanta and Grady Health System medical record. Anyone who has access to your medical records will be able to have access to all the study information placed there. The confidentiality of the study information in your medical record will be protected by laws like the HIPAA privacy rule. State and federal laws may not protect the research information from disclosure.

The results of some study tests and procedures will be used only for research purposes and will *not* be placed in your medical record. For this study, those items include:

- Measurements of biotin-labeled red blood cells in your circulation after transfusion
- Testing for antibodies against biotin-labeled red blood cells

Tests and procedures done at non-Emory, Children's Healthcare of Atlanta and Grady Health System places may not become part of your Emory, Children's Healthcare of Atlanta and Grady Health System, medical record. Also, if you decide to be in this study, it is up to you to let your other health providers know.

In Case of Injury

If you believe you have become ill or injured from this research, you should contact Dr. Yee at telephone number [redacted]. You should also let any health care provider who treats you know that you are in a research study.

If you get ill or injured from being in the study, Emory, Grady Health System and Children's Healthcare of Atlanta will help you to get medical treatment. Neither Emory, Grady Health System and Children's Healthcare of Atlanta nor the sponsor will pay for your medical treatment. Your insurer will be billed for your treatment costs. If you do not have insurance, or if your insurance does not pay, then you will have to pay these costs.

Emory, Grady Health System, Children's Healthcare of Atlanta and the sponsor have not, however, set aside any money to pay you if you are injured as a result of being in this study or to pay for this medical treatment. For Emory, Grady Health System and Children's Healthcare of Atlanta, the only exception is if it is proven that your injury or illness is directly caused by the negligence of an Emory, Grady Health System or Children's Healthcare of Atlanta employee. "Negligence" is the failure to follow a standard duty of care. You do not give up any legal rights you may have by being in this study, including any right to bring a claim for negligence.

Costs

There will be no costs to you for participating in this study, other than basic expenses like transportation. You will not be charged for any of the research activities. If the study procedures result in any medical complications that would not fall under "injury" as discussed above, the cost of treatment for those complications may be charged to you or your insurance.

Withdrawal from the Study

You have the right to leave a study at any time without penalty. The researchers also have the right to stop your participation in this study without your consent for any reason, especially if they believe it is in your best interest or if you were to object to any future changes that may be made in the study plan.

Authorization to Use and Disclose Protected Health Information

The privacy of your health information is important to us. We call your health information that identifies you, your "protected health information" or "PHI." To protect your PHI, we will follow federal and state privacy laws, including the Health Insurance Portability and Accountability Act and regulations (HIPAA). We refer to all of these laws as the "Privacy Rules." Here we let you know how we will use and disclose your PHI for the study.

PHI that Will be Used/Disclosed:

The PHI that we will use or share for the main research study includes:

- Medical information about you including your medical history and present/past medications.
- Results of exams, procedures and tests you have before and during the study.

- Laboratory test results.

Purposes for Which Your PHI Will be Used/Disclosed:
We will use and share your PHI for the conduct and oversight of the research study. We will use and share your PHI to provide you with study related treatment and for payment for such treatment. We will also use and share your PHI to conduct normal business operations. We may share your PHI with other people and places that help us conduct or carry out the study, such as laboratories, data management centers, data monitors, contract research organizations, Institutional Review Boards (IRBs) and other study sites. If you leave the study, we may use your PHI to determine your health, vital status or contact information. We will use and disclose your PHI for the administration and payment of any costs relating to subject injury from the study.

Use and Disclosure of Your Information That is Required by Law:
We will use and disclose your PHI when we are required to do so by law. This includes laws that require us to report child abuse or abuse of elderly or disabled adults.

Authorization to Use PHI is Required to Participate:
By signing this form, you give us permission to use and share your PHI as described in this document. You do not have to sign this form. If you do not sign this form, you may still receive non-research related treatment.

People Who will Use/Disclose Your PHI:
The following people and groups will use and disclose your PHI in connection with the research study:

- The Principal Investigator and the research staff will use and disclose your PHI to conduct the study and give you study related treatment.
- Emory, Grady Health System and Children's Healthcare of Atlanta may use and disclose your PHI to get payment for study related treatment and to run normal business operations.
- The Principal Investigator and research staff will share your PHI with other people and groups to help conduct the study or to provide oversight for the study.
- The following people and groups will use your PHI to make sure the research is done correctly and safely:
    - Emory, Grady Health System and Children's Healthcare of Atlanta offices that are part of the Human Research Participant Protection Program and those that are involved in study administration and billing. These include the Emory, Grady Health System and Children's Healthcare of Atlanta IRBs, the Grady Research Oversight Committee, the Emory Research and Healthcare Compliance Offices, and the Emory Office for Clinical Research
    - NHLBI is the supporterof this study. Theymay use and disclose your PHI to make sure the research is done correctly and to collect and analyze the results of the research. The supporter may disclose your PHI to other people and groups like study monitors to help conduct the study or to provide oversight for the study.
    - Government agencies that regulate the research including: Office for Human Research Protections; Food and Drug Administration.
    - Public health agencies.
    - Research monitors and reviewer.
    - Accreditation agencies.
- Sometimes a Principal Investigator or other researcher moves to a different institution. If this happens, your PHI may be shared with that new institution and their oversight offices. PHI will be shared securely and under a legal agreement to ensure it continues to be used under the terms of this consent and HIPAA authorization.

Expiration of Your Authorization
Your PHI will be used until this research study ends.

Revoking Your Authorization
If you sign this form, at any time later you may revoke (take back) your permission to use your information. If you want to do this, you must contact the study team at: Dr. Marianne Yee [redacted]

At that point, the researchers would not collect any more of your PHI. But they may use or disclose the information you already gave them so they can follow the law, protect your safety, or make sure that the study was done properly and the data is correct. If you revoke your authorization you will not be able to stay in the study.

Other Items You Should Know about Your Privacy
Not all people and entities are covered by the Privacy Rules. HIPAA only applies to health care providers, health care payers, and health care clearinghouses. If we disclose your information to people who are not covered by the Privacy Rules, including HIPAA, then your information won't be protected by the Privacy Rules. People who do not have to follow the Privacy rules can use or disclose your information with others without your permission if they are allowed to do so by the laws that cover them.

To maintain the integrity of this research study, you generally will not have access to your PHI related to this research until the study is complete. When the study ends, and at your request, you generally will have access to your PHI that we maintain in a designated record set. A designated record set is data that includes medical information or billing records that your health care providers use to make decisions about you. If it is necessary for your health care, your health information will be provided to your doctor.

We may remove identifying information from your PHI. Once we do this, the remaining information will not be subject to the Privacy Rules. Information without identifiers may be used or disclosed with other people or organizations for purposes besides this study.

Contact Information
Contact Marianne Yee, MD at [redacted] or [redacted]

- if you have any questions about this study or your part in it,
- if you feel you have had a research-related injury or a bad reaction to the study drug, or
- if you have questions, concerns or complaints about the research

Contact the Emory Institutional Review Board at 404-712-0720 or 877-503-9797 or irb@emory.edu:

- if you have questions about your rights as a research participant.
- if you have questions, concerns or complaints about the research.
- You may also let the IRB know about your experience as a research participant through our Research Participant Survey at http://www.surveymonkey.com/s/6ZDMW75.

If you are patient receiving care from the Grady Health System and you have a question about your rights, you may contact the Office of Research Administration at research@gmh.edu.

Children's Healthcare of Atlanta at Hughes Spalding is owned by the Fulton-DeKalb Hospital Authority (FDHA) and managed by HSOC, Inc., an affiliate of Children's. The FDHA maintains oversight for the Grady Health System. If you are a patient receiving care at Children's Healthcare of Atlanta at Hughes Spalding and have a question about your rights, please contact Sarah Marie Huban, Director of Research Administration at 404-785-7477.

If you are a patient receiving care at Children's Healthcare of Atlanta (other than Hughes Spaulding) and have a question about your rights, please contact Sarah Marie Huban, Director of Research Administration at 404-785-7477.

Consent and Authorization

TO BE FILLED OUT BY SUBJECT ONLY

Please **print** your name, **sign**, and **date** below if you agree to be in this research study. By signing this consent and authorization form, you will not give up any of your legal rights. We will give you a copy of the signed form to keep.

_____

Name of Subject

_____ _____

Signature of Subject (18 or older and able to consent) **Date** **Time**

_____ _____

Signature of Legally Authorized Representative **Date** **Time**

_____

Authority of Legally Authorized Representative or Relationship to Subject

Optional Consent to receive communication about upcoming study visit date reminders by email or text messaging

□ _____ *(initial) I consent to receive email or text message reminders for this study.*

□ _____ *(initial) I do **not** consent to receive email or text message reminders for this study.*

Optional Consent to receive a repeat biotin-labeled transfusion at a later time point. This option might be discussed after you complete the study visits (6 months or more after the first biotin-labeled transfusion), and if you have had no adverse events related to the study transfusion.

□ _____ *(initial) I consent to be offered participation in a repeat biotin-labeled transfusion at a later time point.*

□ _____ *(initial) I do **not** consent to be offered participation in a repeat biotin-labeled transfusion at a later time point.*

TO BE FILLED OUT BY STUDY TEAM ONLY

_____

Name of Person Conducting Informed Consent Discussion

_____ _____

Signature of Person Conducting Informed Consent Discussion **Date** **Time**

Optional Study Information

Your data and/or specimens will be protected the same way as the data and/or specimens for the main study.

What is the purpose of this study?
The purpose of this research is to study the survival of transfused red blood cells that have been treated with a pathogen reduction technology, in patients with sickle cell disease or thalassemia. The pathogen reduction system used in this optional study is called the INTERCEPT Blood System for Red Blood Cells. The INTERCEPT system is investigational. The system was designed to make red blood cell transfusions safer by inactivating germs (bacteria, viruses, etc.) that might be present in a red blood cell unit even after it has been tested.

In this study we would like to measure how long a red blood cell (RBC) transfusion that has been treated with the INTERCEPT Blood System for RBCs survives in your blood. We will do this at a time when you normally would be receiving a RBC transfusion for your sickle cell disease or thalassemia treatment. The blood units that you receive for 1 transfusion will have a small "label" added to them in the laboratory before transfusion. The label we will use is biotin, which is a naturally occurring vitamin that most people eat large amounts of every day. This type of labeling, which is for investigational purposes, has been used for many years and has been shown to be very safe even when used in very young babies. This label allows us to measure the transfused RBC in your blood samples for weeks after the transfusion.

The INTERCEPT treatment process also adds a different kind of "label" to treated RBCs. These labels are called acridine. Acridine labeling on RBCs is a side effect of the INTERCEPT treatment process. It has been studied in several clinical trials in Europe and the United States. Researchers believe acridine labels on RBCs are safe. This study will also track these acridine labels over time to see if they can be used as a second way (in addition to biotin labels) of measuring how long RBCs survive in a person after a transfusion.

What will I be asked to do?
These procedures are in addition to what is being asked of you in the main study.

Before Transfusion: If you decided to participate in this study, we will take some of your blood that would otherwise be thrown away and use it to look for antibodies to RBCs treated with the INTERCEPT Blood System for RBCs (also called INTERCEPT RBCs). 1 to 3 days before your transfusion we will repeat the test to look for antibodies to INTERCEPT RBCs. These tests will be done on blood drawn for a routine crossmatch test, so a separate blood draw will not be required. If you do not have antibodies to INTERCEPT RBCs, you will be able to participate in this optional study if you choose. If you have antibodies to INTERCEPT RBCs you will not be able to participate in this optional study. If you have antibodies to INTERCEPT RBCs you will be eligible for follow-up testing by Cerus, the company that developed the INTERCEPT Blood System, to determine if the naturally occurring antibody is a risk to your health. This follow-up testing is also optional. It is offered to you as a free benefit.

Transfusion: You will come to clinic to receive one of your regular chronic transfusions. On this day a small amount (20 mL) of the INTERCEPT RBCs will be labeled with biotin and stored in a syringe. A second syringe with 20 mL of blood from the same donation as the INTERCEPT RBCs, but which has not been treated with the INTERCEPT system, will also be labeled with biotin. The purpose of this second syringe is to study any differences between blood that has been treated with the INTERCEPT system and blood that has not been treated with the INTERCEPT system. The two 20 mL syringes will be transfused after the main INTERCEPT RBC unit is transfused. These 2 syringes will be the only transfusion with labeled blood you will receive as part of this optional study.

If you need more than one RBC unit on the day you participate in this optional study, you will receive regular RBCs that have not been treated with the INTERCEPT system from the Children's Healthcare or Grady Healthsystem blood bank.

After Transfusion: If you decided to participate in this optional study there will be no additional blood draws or visits. We will take a small amount of additional blood (5mls or 1 teaspoon) when you are already coming in for the main study. We will collect this extra blood at the following timepoints:

- Right after the transfusion is complete
- 24 Hours after the transfusion is complete
- Every week for the first 2 weeks after transfusion
- Every other week for weeks 4, 6, 8, 10 and 12
- 6 months after the transfusion

If at week 12 you still have biotin-labeled RBC detected in your blood samples and you choose to give a blood sample once a week (at week 13, week 14, week 15, and week 16) until 16 weeks after the transfusion for the main study we would like to get an extra blood sample (5mls or 1 teaspoon) for this optional study at week 14 and week 16.

Whenever possible, we will do the blood sample at the same time that you are doing other routine blood work for your sickle cell or thalassemia health care.

Some of the blood collected for this optional study will be frozen and shipped to the Cerus Corporation laboratory in Concord, CA for specialized testing to track the survival of INTERCEPT RBCs using the acridine labels described above. These samples and all of the data (for example, PHI) associated with them will be protected under a legal agreement between Emory and Cerus.

If at any time after the INTERCEPT RBC transfusion you develop an antibody that is specific to INTERCEPT RBCs, you will be offered additional testing free-of-charge by Cerus to determine whether the antibody is harmful to you. Antibodies that are specific to INTERCEPT RBCs have been detected in about 0.1% of patients who have participated in other clinical trials with INTERCEPT RBCs. They are very rare. These antibodies have also not been clinically significant (the patients only knew they had them because of the testing) and they generally faded away after about 6 months. Cerus offers additional testing to patients who develop these antibodies so that researchers can better understand how these rare and harmless antibodies develop and fade away.

If you participate in the extra testing for an INTERCEPT RBC antibody (if you develop one), we will ask you to come in for an extra blood draw where we will take 15mls to 45mls (3 teaspoons to 3 tablespoons) depending on how much you weigh. These samples will be sent to the Cerus laboratory for testing. These specimens and associated data will also be protected by a legal agreement between Emory and Cerus.

What are the possible risks and discomforts?

Risk of transfusion with INTERCEPT RBCs:

Blood transfusions are generally considered to be safe and are part of your regular sickle cell or thalassemia health care. Risks of blood transfusions include fever, skin rash or hives, allergy, and infection. We do not think that there will be an increase in these reactions if you are transfused with INTERCEPT RBCs.

INTERCEPT RBCs are treated with a chemical compound called amustaline dihydrochloride. Amustaline dihydrochloride is capable of inactivating many types of pathogens making them unable to cause infection from transfusion of red blood cells. Amustaline dihydrochloride acts by causing changes to the pathogens, which inactivate them and prevents them from growing. As red blood cells do not contain DNA or RNA, which is the target of the amustaline dihydrochloride in pathogens, the amustaline dihydrochloride is not expected to affect them.

Amustaline dihydrochloride comes from a group of substances with a chemical structure similar to compounds used to

treat some types of cancer. After it is added to red blood cells, it is designed to "self-destruct" in a short period of time. The majority of amustaline dihydrochloride is destroyed during treatment (prior to transfusion), but a tiny quantity may be found in the red blood cells once the process is complete. Nevertheless, this quantity is small enough to be insignificant. The red blood cells treated with amustaline dihydrochloride have been tested in various tests run on animals to evaluate clinical safety. The longest trial lasted 9 months. The animals received weekly transfusions. There were no signs of unusual or abnormal health effects in any of the animals tested. A special trial was conducted on animals to see whether the INTERCEPT treated red blood cells and the amustaline breakdown products can cause tumors. The animals received up to 1000 times the quantity of amustaline breakdown product that your child will receive. The study showed that exposure to INTERCEPT treated red blood cells and the amustaline dihydrochloride breakdown product did not cause cancer in lab animals.

The INTERCEPT treated red blood cells will be preserved in SAG-M, a sugar-salt solution regularly used in Europe for preserving red blood cells. There are no known risks associated with its use in this manner.

The INTERCEPT Blood System for Red Blood Cells consists of a series of sterile plastic containers that are connected to keep the system sterile. The plastic materials that the INTERCEPT Blood System containers are made of have been used in other medical devices approved for contact with blood products or solutions administered into the bloodstream. There is no known risk increase associated with the use of this plastic system.

As mentioned above, a possible known risk linked to INTERCEPT treated red blood cell transfusions is an immune (allergic) reaction. This type of reaction was encountered in an earlier study with a previous version of the INTERCEPT Blood System for Red Blood Cells (referred to as “first generation process”). The two patients in this earlier study developed antibodies against a part of the amustaline dihydrochloride compound. No abnormal health effects were seen in these participants and the antibodies disappeared in 6 months. Antibodies form when a person’s immune system recognizes and defends itself against foreign substances like viruses, bacteria or chemical substances. For example, some patients produce antibodies against antibiotics, like penicillin.

After having observed the antibody response in these participants, Cerus conducted further research and changed the INTERCEPT Blood System for Red Blood Cells in order to reduce the quantity of amustaline dihydrochloride on the surface of the treated red blood cells. In fact, lab tests show that the red blood cells treated with this further optimized next generation process called the “current process” are less likely to cause an amustaline dihydrochloride immune reaction when transfused.

Tests on animals given transfusions of INTERCEPT treated red blood cells did not show any signs of immune or allergic reactions. Tests were run on human beings to assess how well the red blood cells work and survive in circulation after transfusion. These tests showed that the INTERCEPT treated red blood cells function normally. In this Cerus study in the US, some patients have developed antibodies to INTERCEPT red blood cells. In response, Cerus stopped their participation in the study, followed them over time, monitored their health, and found there were no harmful side effects. Cerus notified the committee who oversee safety for the study patients (called the “Data Safety Monitoring Board” or DSMB). The committee reviewed the findings and determined the study could continue to enroll new patients into the study.

There may be side effects from the study or procedures that are not known at this time.

It is possible that the researchers will learn something new during the study about the risks of being in it. If this happens, they will tell you about it. Then you can decide if you want to continue to be in this study or not. You may be asked to sign a new consent form that includes the new information if you decide to stay in the study.

Will I benefit directly from the study?

This optional study is not designed to benefit you directly. However, a possible benefit is reduced risk of diseases transmitted by transfusion while your child is receiving INTERCEPT treated red blood cells. There is also a chance the risk of reactions to transfusion is reduced, since the transfused blood contains less plasma. Plasma is a part of the blood that contains the substances (proteins) the immune system could recognize as foreign and could therefore cause a reaction to the transfusion. This study is designed to learn more about how long pathogen reduced RBCs survive in the body after they are transfused. The study results may be used to help others in the future.

Will I be compensated for my time and effort?

In addition to the compensation you receive for the main study, you will receive $50 for each of the following visits - Pre Transfusion, Transfusion and for the 24 hour Post Transfusion. You will receive $25 for each of the 8 visits that are required for this optional study to compensate you for your time and effort. If you do not finish the optional substudy, we will compensate you for the visits you have completed. You will get $350 total, if you complete all required optional substudy visits.

If you still have biotin-labeled RBC detected in your blood samples by 12 weeks and you choose to give a blood sample at weeks 14 and 16 after the transfusion you will receive $25 for each additional visit to compensate you for your time and effort. If you do not finish the additional study visits, we will still compensate you for the visits you have completed. If you complete all 2 extra study visits, you will receive an additional $50. This would make the total compensation from the optional substudy up to $400.

You will be reimbursed for transportation in the same way as the main study.

You will be asked to fill out a tax form, including your Social Security or Taxpayer Identification Number, in order to be reimbursed, if joining the substudy increases your annual compensation over the taxable amount.

What are my other options?

You can participate in the main study and not take part in this optional study. You can also decide not to participate in either study.

Withdrawal from the Optional Study

You have the right to leave this optional study at any time without penalty. You may stay in the main study even if you leave this optional study.

The researchers also have the right to stop your participation in this optional study without your consent for any reason, especially if they believe it is in your best interest or if you were to object to any future changes that may be made in the study plan.

Contact Information

See contact information for the main study, above.

HIPAA Authorization for Optional Study

You do not have to authorize the use and disclosure of your PHI for the optional study. If you do not, you can still be in the main research study.

Your PHI will be used in the Optional substudy the same way it will be used and disclosed for the main study, with the following differences:

- The following types of PHI may be used or disclosed for the optional substudy:

- Medical information about your child including your child's medical history and present/past medications.
- Results of exams, procedures and tests your child has before and during the study.
- Laboratory test results.

- The purpose of the use and disclosure is for the optional substudy described above
- The following *additional* people may use or disclose your PHI:
  - Cerus is the supporterof this optional study. The supporter may use and disclose your child's PHI to make sure the research is done correctly and to collect and analyze the results of the research. The supporter may disclose your child's PHI to other people and groups like study monitors to help conduct the study or to provide oversight for the study.

Consent and Authorization

TO BE FILLED OUT BY SUBJECT ONLY

Please **print** your name, **sign**, and **date** below if you agree to be in the optional study described above. By signing this form, you will not give up any of your legal rights. We will give you a copy of the signed form to keep.

_____

Name of Subject

_____ _____

Signature of Subject (18 or older and able to consent) **Date** **Time**

_____ _____

Signature of Legally Authorized Representative **Date** **Time**

_____

Authority of Legally Authorized Representative or Relationship to Subject

TO BE FILLED OUT BY STUDY TEAM ONLY

_____

Name of Person Conducting Informed Consent Discussion

_____ _____

Signature of Person Conducting Informed Consent Discussion **Date** **Time**