University of Pittsburgh

School of Medicine
UPMC Vascular Medicine Institute

CONSENT TO ACT AS A PARTICIPANT IN A RESEARCH STUDY

TITLE: Transfusion of Biotin-Labeled Red Blood Cells for the Evaluation of Genetic Factors that Contribute to Donor Differences in Red Blood Cell Storage and Post-Transfusion Red Blood Cell Recovery

PRINCIPAL INVESTIGATOR:	
	Darrell Triulzi, MD Director of the Division of Transfusion Medicine, Department of Pathology, UPMC and Medical Director, Clinical Services Vitalant-Pittsburgh 3636 Blvd. of the Allies Pittsburgh, PA 15213 412-209-7304
Study Coordinator	
Carolyn Newkirk Vascular Medicine Institute 412-692-2437	
SOURCE OF SUPPORT: NIH/NHLBI - Storage Lesion Grant- Mark Gladwin, MD	

Key Information - Research Study

STUDY TITLE: Transfusion of Biotin-Labeled Red Blood Cells for the Evaluation of Genetic Factors that Contribute to Donor Differences in Red Blood Cell Storage and Post-Transfusion Red Blood Cell Recovery

You are being asked to take part in a research study. Research studies include only people who choose to take part. The study team members will explain the study to you and will answer any questions you might have. You should take your time to make your decision.

- The purpose of this study is to see if adding the naturally occurring vitamin biotin to donated blood will impact the survival of red blood cells. The way we test it is by taking a blood donation from the research volunteer, taking out the red blood cells, treating them with biotin and infusing them back into the person. In addition, this study is to see if genes related to sickle cell disease and other metabolic inherited disorders may affect red blood cell survival after storing the blood and transfusing it back into the person. We

will be enrolling several subgroups to see if there is a difference based on genetics, gender or race. The study will last about 8 months with about 10 visits to UPMC Montefiore and including 1 at the blood bank.
- Study procedures include blood donation, blood draws, and vital signs.

Risks and side effects related to the study while receiving biotin-labeled blood include:
- a transfusion reaction (rare) such as fever, chills, nausea/vomiting, itching, rash, hives, hemolysis, shortness of breath,
- changes in blood pressure (high and low) and anaphylaxis, antibodies to biotin – but these do not develop into health problems,
- those related to blood collection pain, nausea, fainting or dizziness, low blood pressure, bruise at needle puncture site, possible nerve damage, blood loss and infection
- those related to confidentiality – small risk of information being disclosed.

These risks will be reviewed in much more detail on the following pages.
You will be compensated $840 if you complete all study visits.

There is no direct benefit to you associated with your participation in the study; however, there may be a potential future benefit to society as a whole, from the information obtained from the conduct of this study through the advancement of knowledge.

We invite you to take part in the research study. First, we want you to know that taking part in this research study is entirely voluntary. You may choose not to take part, or you may withdraw from the study at any time. You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, 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). If you have such beliefs, please discuss them with your doctors or research teams before you agree to the study.

A description of this clinical trial will be available on www.clinicaltrials.gov, as required by US Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

Why is this research being done?
This study will look at the process of blood donation and storage. When you donate a unit of blood, it is stored in a blood bank for up to 6 weeks. There have been clinical trials that suggest that the longer time the blood is stored, the more the blood changes. The purpose of this study is to see if adding the naturally occurring vitamin biotin to donated blood will impact the survival of red blood cells. The way we test it is by taking a blood donation from the research volunteer, taking out the red blood cells, treating them with biotin and infusing them back into the person. In addition, this study is to see if genes related to sickle cell disease and other metabolic inherited disorders may affect red blood cell survival after storing the blood and transfusing it back into the person. We will be enrolling several subgroups to see if there is a difference based on genetics, gender or race. The subgroups include:
- men on testosterone therapy
- people with sickle cell disease

- differences between men and women
- differences by race
- people with rare diseases

You may fit into one of these subgroups. We will also compare data from samples in this study to stored samples from other studies.

Who is being asked to take part in this research study?
Up to 175 healthy volunteers, ages 18 and older fitting in one of our five subgroups are expected to be enrolled in this study. We are asking you to participate in this research study because you are a non-smoker with no history of anemia (or have too few red blood cells) and, if female, are not pregnant. If you are male or female, you must weigh110 pounds or greater.

You have already successfully completed a telephone screening interview and will need to complete an onsite screening visit, to be sure that you have no conditions or illnesses that could stop you from undergoing study procedures.

What procedures will be performed for research purposes?
This study will last about 8 months involving ten (10) study visits. These visits will include:

- a screening visit,
- a blood donation visit where we put in an IV to remove some blood to store,
- two (2) transfusion days where we put your blood with biotin added to it back into your circulation and,
- six (6) follow up visits.

The blood donation visit will occur within 4 weeks of your screening visit. The first transfusion day will occur within approximately 5-7 days of your blood donation visit and the second transfusion day will occur within approximately 35-42 days after your blood donation visit. We will ask you to come in approximately 24 hours after each transfusion visit for a blood draw. You will have one follow-up visit in between the two transfusion visits, approximately 32-41 days after the completion of the first transfusion. The last three (3) visits will occur approximately 1 month post the second transfusion, 2 months post the 2nd transfusion and 3-4 months post the 2nd transfusion.

SCREENING PROCEDURES (Visit 1):
A screening visit will be scheduled during the telephone pre-screening conversation with the study coordinator and you. We will ask you not to eat anything from the night prior to arriving to the testing center. We will ask you to fast for at least 8 hours prior to study visit. This screening visit will take place in the Clinical and Translational Research Center (CTRC) located on the 6th floor of UPMC Montefiore, which will include a review of the study and this consent document.

The investigator or study team member will discuss the nature of the research study, the risks of study participation, and your rights as a research subject. After allowing you plenty of time to review the information, the investigator or co-investigator, who is a physician, will answer any questions and will then ask you to sign an informed consent that means you agree to participate in the study. Even if you sign this you can choose to leave the study at any time. If you have decided to take part in this study and have read and reviewed this consent form, we will perform the following procedures:

We will ask you questions and test your blood to determine if you are allowed to take part in a research study. These are called “screening” procedures. No research related procedures pertaining to this study will be performed prior to your signing consent. The screening procedures are listed below:

- We will ask you questions concerning all medications prescriptions and non-prescription medications (vitamins, herbal supplements, aspirin, etc.) that you are presently taking. We will ask if you have donated blood within the past 56 days. We will be recording all this information to your research record.

- We will take your medical history and do a physical examination by the study doctor.

- If you are female of child bearing potential, we will do a urine pregnancy dip test. If the test result is positive, you will not be able to participate in the study.

- We will record your height, weight and vital signs (temperature, heart rate, respiratory rate, blood pressure, pulse oximetry- which is a test that shows how much oxygen is in your blood – involves putting a soft clip on the tip of your finger)

- We will draw blood for laboratory testing. These tests will be a complete blood count (a test to make sure that you are not anemic, or have too few red blood cells), creatinine (to check kidney function), ALT, AST (check for liver function), lipids (tests that measure fats that are in your blood), and hemoglobin A1C (a test to measure your average blood sugar level in the last 2-3 months. We will collect blood to test for different types of proteins in your red blood cells and check to see if your blood has antibodies that can destroy your own red blood cells. These tests will be performed to evaluate the health of your body during study participation. We will also collect a research sample to test for antibodies to BioRBCs. This would show that your body would reject the blood when we would give it back to you. We will collect blood for a type and cross (test to make sure you are receiving correct blood for transfusion). We may collect another blood sample which is called a check-type sample. This test is required by Vitalant to double check that you will receive the correct blood for the transfusion

- We may draw a sample of your blood to screen your blood for the sickle cell trait. You will be promptly notified if the study team discovers that you have the sickle cell trait during the conduct of this research study that may cause you to change your mind about continuing to participate.

- We will take a blood sample from you to test for single nucleotide polymorphisms. We will analyze your blood samples for genes related to sickle cell disease and other metabolic inherited disorders. The analysis will look for “SNPs” which stands for single nucleotide polymorphism. A SNP is a difference in a single building block of a gene. This means it is a part of a gene. Your genetic results will not be shared with you because they will need additional research before their clinical significance is understood. We will not take a blood sample from blood donors of the NHLBI’s RBC-Omics study. We will collect approximately 3 tablespoons of blood for these samples.

All your screening results will be reviewed by the study physician prior to the Blood Donation Day visit. You will be provided with any abnormal screening results so that you can follow up with your primary care doctor for further evaluation. It is possible that after taking these tests you may not be able to take part in this study. The total duration of this visit is approximately 1 ½-2 hours.

If you have an abnormal blood test that makes you ineligible for this study, we may ask you to return to repeat it. The study doctors may think that:

1. it is due to an error in laboratory processing (such as the process causing the blood cells to burst or,
2. the laboratory accidentally mixing your sample up with another person's, or,
3. it will be normal if repeated (in the case that you have a reversible cause of a low blood count or are dehydrated causing your kidney labs to be abnormal).

Then we may ask you to return to the CTRC for a second blood draw of only the abnormal blood work. You will be paid for this added visit. If you decide not to return for this additional blood work, your original abnormal blood work will be used to decide if you are eligible for the study. Any abnormal lab tests will likely exclude you from the study, however the study doctors reserve the right to determine whether abnormal laboratory values will exclude you from the study or not.

Once these screening procedures are completed and we find out that you can participate in the study, the research coordinator will call you to return at a scheduled time for the blood donation portion of the trial. This blood donation visit will occur within approximately 4 weeks of your screening visit.

EXPERIMENTAL RESEARCH PROCEDURES

Blood Donation Visit (Visit 2):

The blood donation visit will be scheduled within approximately 4 weeks of Visit 1 at Vitalant Pittsburgh. For this visit, the research coordinator will schedule with you an agreed upon appointment date and time to report to the Vitalant Pittsburgh blood bank for you to donate one unit of blood. You should not have donated blood within 56 days prior to this screening visit. The procedure for the collection of blood is done routinely at Vitalant Pittsburgh blood bank by their professionally trained staff. The blood bank personnel will take time to discuss the process for this procedure and ask you to review and complete an extra informed consent document for blood donation. Your private health information will be given to Vitalant staff members in order for your blood to be released to the HSCLab and to make sure that you receive the correct blood for your transfusion visits. Your private information will be given to Vitalant via UPMC secure email with a study ID. Every effort will be made to keep this information confidential.

After signing the blood bank informed consent for this procedure the blood bank staff will ask you standard questions that all blood donors are asked, including the standard donor health history questions, and they will collect information on your height, weight, gender, and obtain vital signs. This is important information that is required for standard blood donation procedures.

One unit, approximately 500 mL (2 cups) of your blood will be collected into a bag through an IV inserted in your arm. This procedure is done according to strict FDA and American Association

of Blood Banks (AABB) requirements. Using standard FDA and AABB approved procedures we will test, process, and label, with your name, your one unit of blood that is collected from this procedure. Your blood will be tested for HIV, hepatitis C virus, hepatitis B virus and other viruses as part of standard blood donation procedure. These results are maintained in a confidential manner at the blood bank and will only be shared with you and if applicable, required health authorities. We want you to know that the State of Pennsylvania requires the blood bank to report positive results for HIV, Hepatitis C virus, Hepatitis B virus, West Nile Virus, HTLV, Chagas, Zika and Syphilis. You will be informed of abnormal results according to standard blood banking practices. The unit of blood will be stored in a monitored blood bank refrigerator under standard conditions within the registered transfusion service at UPMC Shadyside hospital until needed for the study testing days. The stored blood will be under the supervision of the Blood Bank Medical Director, Darrell Triulzi, M.D. The total duration of this blood donation visit is approximately 1-2 hours. As with normal volunteer donors, blood donors must wait approximately 8 weeks (56 days) before they are allowed to donate blood again.

The release of the blood for transfusion by the blood bank will inform the investigators that you have tested negative for the infectious diseases described above. If the blood is not released by the blood bank, this will inform investigators that you may have tested positive for one of the infectious diseases described above. The investigators will not be informed of what test may be positive. You will be informed of abnormal results according to the standard blood bank practices. Once this blood donation visit has been completed, the research coordinator will contact you by phone to schedule your first transfusion visit that will take place within 5-7 days of this visit.

*Visits 4,5 , 7, 8, 9, and 10 will last approximately 30-90 minutes. The blood transfusion visits (visits 3 and 6) will last approximately 4 to 6 hours.

1st Transfusion (Visit 3):
This visit will be scheduled between approximately 5-7 days following your blood donation visit and will take place in the CTRC. You do not need to fast prior to coming in for your appointment. Your private health information and study ID number will be given to HSCLab staff members via UPMC secure email system in order for your blood to be released to CTRC and to make sure that your receive the correct blood on the day of your transfusion visit. Every effort will be made to keep this information confidential.

The following procedures will take place:

- Brief physical exam
- Vital signs (temperature, heartrate, respiratory rate, blood pressure, pulse oximetry)
- Urine pregnancy test in women of childbearing potential
- Blood draw for clinical lab testing (CBC)
- Blood draw to make sure you do not have any BioRBC's
- We will give you back some of your blood that we stored in the blood bank for 5-7 days labeled with the vitamin, biotin, as an infusion into your arm vein. The use of biotin-labelled (called "biotinylated") red blood cells has not been approved by the FDA.
- Collect leftover BioRBCs in unit of blood/IV line for testing blood storage
- We will check your vital signs about every 15 minutes during the transfusion and about 15 minutes after the transfusion
- We will draw another blood sample to check your baseline for survival of 5-7 day old

BioRBCs about 2-4 hours after the transfusion.
- Monitor for any adverse events
- You will be given a meal and then discharged.

Total blood volume drawn will be about 2 tablespoons.

Visit 4:
This visit will take place in MUH-CTRC and be scheduled approximately 24 hours after the first blood transfusion visit.
- Blood draw approximately 24 hours after the first transfusion visit to test survival of BioRBCs
- Blood draw for clinical lab testing (CBC)
- Montior for any adverse events

Total blood volume drawn will be about 1 tablespoon.

Visit 5:
This visit will be scheduled approximately alittle over one month (ranges between 31-42 days) after completion of 1st transfusion in MUH-CTRC or MUH-TRC 8th floor. You do not need to fast prior to coming in for your appointment.
- Blood draw to test antibodies to BioRBCs. If anti-BioRBC antibodies are found following the 1st transfusion, you will be withdrawn from the study. You will need to have a negative test to continue with the study.
- Blood draw for Type and Cross prior to transfusion.
- Monitor for any adverse events

Total blood volume drawn will be about 1 tablespoon.

2nd Transfusion (Visit 6):
This visit will be scheduled between approximately 35-42 days following your blood donation visit and will take place in the CTRC. You do not need to fast prior to coming in to your appointment. Your private health information and study ID number will be given to HSCLab staff members via UPMC secure email system in order for your blood to be released to CTRC and to make sure that your receive the correct blood on the day of your transfusion visit. Every effort will be made to keep this information confidential.
The following procedures will take place:
- Brief physical exam (review medical history and demographics)
- Vital signs (temperature, heartrate, respiratory rate, blood pressure, pulse oximetry)
- Urine pregnancy test in women of childbearing potential
- Blood draw for clinical lab testing (CBC)
- Blood draw to make sure you do not have any BioRBC's
- We will give you back some of your blood that we stored in the blood bank for 35-42 days labeled with the vitamin, biotin, as an infusion into your arm vein.
- Collect leftover BioRBCs in unit of blood/IV line for testing blood storage
- We will check your vital signs about every 15 minutes during the transfusion and about 15 minutes after the transfusion
- We will draw another blood sample to check your baseline for survival of 35-42 day old

BioRBCs about 2-4 hours after the transfusion.
- Monitor for any adverse events
- You will be given a meal and then discharged

Total blood volume drawn will be about 2 tablespoons.

Visit 7:
This visit will take place in MUH-CTRC and be scheduled approximately 24 hours after the second blood transfusion visit.
- Blood draw approximately 24 hours after second transfusion visit to test survival of BioRBCs
- Blood draw for clinical lab testing (CBC)
- Monitor for any adverse events

Total blood volume drawn will be about 1 tablespoon.

Visit 8:
This visit will be scheduled between approximately 65-72 days (this will be approximately 1 month after the completion of the 2nd transfusion). This visit will take place in the CTRC or MUH-TRC 8th floor. You do not need to fast prior to coming in. The following procedures will take place:
- Vital signs (temperature, heartrate, respiratory rate, blood pressure, pulse oximetry)
- Blood draw to determine BioRBC survival
- Blood draw for clinical lab testing (CBC)
- We will draw another blood sample to check for antibodies to BioRBCs
- Monitor for any adverse events

Total blood volume drawn will be about 1 tablespoon.

Visit 9:
This visit will be scheduled between approximately 95-102 (this will be approximately 2 months after the completion of the 2nd transfusion). This visit will take place in the CTRC or MUH-TRC 8th floor. You do not need to fast prior to coming in. The following procedures will take place:
- Vital signs (temperature, heartrate, respiratory rate, blood pressure, pulse oximetry)
- Blood draw to determine BioRBC survival
- Blood draw for clinical lab testing (CBC)
- Monitor for any adverse events

Total blood volume drawn will be about 1 tablespoon.

Visit 10:
This visit will be scheduled between approximately 125-150 days (this will be approximately 3-4 months after the completion of the 2nd transfusion). This visit will take place in the CTRC or MUH-TRC 8th floor. You do not need to fast prior to coming in. The following procedures will take place:
- Vital signs (temperature, heartrate, respiratory rate, blood pressure, pulse oximetry)
- Blood draw to determine BioRBC survival

- Blood draw for clinical lab testing (CBC)
- We will draw another blood sample to check for antibodies to BioRBCs
- Monitor for any adverse events

Total blood volume drawn will be about 1 tablespoon.

Additional blood draws
You may be asked to return to the CTRC periodically over the next 3 months for further blood draws important for the biotinylation analysis of your blood cells. The total volume will not exceed a total of 2 tablespoons.You will be compensated an additional $50 each time you are asked to return for a blood draw.

What side effects or risks can I expect from being in this research study?
As with any experimental procedure, there may be adverse events or side effects that are currently unknown and certain of these unknown risks could be permanent, severe, or even life threatening.

Risk of Autologous Blood Transfusion: Autologous (your own) blood transfusion is associated with fewer risks than allogeneic (someone else's) blood from a volunteer donor. On the 6th week of storage, the red blood cells can breakdown and disruption of iron (the important element of blood production) is reported as a potential risk of using your own blood during the transfusion. Autologous blood avoids the risk of transmitting a viral infection with the transfusion or having an immune reaction to the transfusion. In this study, you only receive a small volume of autologous packed BioRBCs. The risk of experiencing a transfusion reaction is considered minimal; no excess risk of transfusion reactions is expected from the small autologous infusions used in this study. However, transfusions of conventional blood products are known to be associated with adverse transfusion reactions such as fever, chills, nausea/vomiting, itching, rash, hives, hemolysis, shortness of breath, changes in blood pressure (high and low) and anaphylaxis. Anaphylaxis is a severe, potentially life-threatening allergic reaction and may include your blood pressure dropping suddenly and your breathing tubes to your lungs narrowing and blocking breathing. This is a rare risk.

Risks of BioRBC Infusion: Infused biotin-labeled red blood cells may be rejected and cleared from your blood circulation. However, because the amount of infused biotin-labeled red blood cells in the circulation is very small (about 2% of total blood volume), removal of these cells is not likely to cause any health problems. Processing and labeling red blood cells with biotin is done under sterile conditions, however, there is a minimal risk of bacterial contamination that may cause infection. This risk is reduced by testing each blood for contamination before infusion.

Risk of Antibody Formation: Your body may develop an immune response (create antibodies) to biotin. Rare events may include destruction of transfused biotinylated red blood cells. In a similar study, 3 of 20 (15%) adult volunteers had developed antibodies to biotin-labeled red blood cells, but none developed anemia or any other health problems, and the antibodies disappeared from the circulation within months. To reduce this risk of antibody formation, a lower dose of biotin is used throughout this study compared to the previous study, and subjects will be screened for antibody formation after infusions and during follow-up visits

Risk of Whole Blood Collection: Whole blood collection is a term for blood donation. The risks involved in whole blood donation include nausea, fainting or dizziness, low blood pressure, bruise at needle puncture site, possible nerve damage, blood loss and infection. Other less common risks include IV insertion complications and fainting (vasovagal) reactions. These risks are explained at the time of donation. Study subjects will be required to meet all FDA and AABB defined volunteer donor criteria prior to donating blood to the bank for this study. If your blood is identified to be positive for HIV, Hepatitis C virus, Hepatitis B virus, West Nile Virus, HTLV, Chagas, Zika and Syphilis it will be reported to the PA Dept. of Health.

Risks of Venipuncture /Intravenous Needle Tube Insertion: To minimize the risks of blood tests an RN, MD, technician or phlebotomist will draw your blood. Common risks of blood sampling by venipuncture or intravenous line placement include temporary pain, bruising which may last for several days, redness, swelling and phlebitis. Infrequent risks include feeling lightheaded or faint when blood is drawn. This is usually due to nervousness (not due to the amount of blood taken), and it is not usually serious. Infrequent risks for the intravenous line include infiltration (a leakage of anything that has been given through the vein (such as the saline,) into the arm tissue that surrounds the vein and holds the IV). Rare risks include infection and bleeding.

Reproductive Risks
Biotin-labeled blood has not been tested before so we are unsure if it can affect an unborn baby; however, the vitamin biotin is used during pregnancy in a pill form taken by mouth to supplement when there is a biotin deficiency.

Risk of Collection of Private health information and biospecimens
Although we are taking many steps to protect your information, there is always a rare chance that your information or identity could be disclosed. We will continue to review and improve the ways we keep your information private. To protect your information, paper-based records will be kept in a secure location and only be accessible to personnel involved in the study. Paper charts will contain subject identifiers but will be in locked cabinets within a locked office on a unit that has restricted access.

Risks of Genetic Analysis
The risks associated with genetic studies include the potential for a breach of confidentiality which could affect future insurability, employability, or reproduction plans, or have a negative impact on family relationships and/or result in paternity suits or stigmatization.

A Federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies and group health plans to use genetic information in making decisions regarding your eligibility or premiums. GINA also makes it illegal for employers with 15 or more employees to use your genetic information when making decisions regarding hiring, promoting, firing, or setting the terms of employment. This new Federal law does not protect you against genetic discrimination by companies that sell life, disability, or long-term care insurance.

May I withdraw, at a future date, my consent for participation in this research study?
You may withdraw, at any time, your consent for participation in this research study, to include

the use and disclosure of your identifiable information for the purposes described above. (Note, however, that if you withdraw your consent for the use and disclosure of your identifiable medical record information for the purposes described above, you will also be withdrawn, in general, from further participation in this research study). Any identifiable research or medical information recorded from your participation in this research study prior to the date that you formally withdraw your participation may continue to be used and disclosed by the investigators for the purposes described above.

Your data and biological samples will be stored for future research analyses and may be shared with other researchers or federal repositories. We will share your de-identfied biological samples with Wake Forest University for research analyses. They will be stored indefinitely unless you request for the samples to be destroyed. Your samples will not be labeled with direct identifiers. Your identity on these samples and records will be indicated by a random case number, rather than by your name, social security number or any other label that could identify you. There is no plan presently, but these samples may undergo further genetic testing, including whole genome sequencing, which is the entire genetic code determined by biological parents.
To formally withdraw your consent for participation in this research study, you should provide a written and dated notice of this decision to the principal investigator of this research study at the address listed on the first page of this form.

Your decision to withdraw your consent for participation in this research study will have no effect on your current or future medical care at a UPMC hospital or affiliated health care provider or your current or future relationship with a health care insurance provider.

Does this research study include whole genome sequencing?
Your participation in this study may include whole genome sequencing.

If I agree to take part in this research study, can I be removed from the study without my consent?
You may be removed from the study by the investigators in the event that the investigators feel that the study may adversely influence your health; if you don't comply with study requirements; if a pregnancy test proves positive; you develop a severe, acute illness during the study period; or other situation at Dr.Triulzi's discretion.

Any identifiable research or medical information recorded for, or resulting from your participation in this research study prior to the date that you were withdrawn from participation may continue to be used and disclosed by the investigators for the purposes described.

If I agree to take part in this research study, will I be told of any new risks that may be found during the course of the study?
You will be promptly notified if any new information develops during the conduct of this research study that may cause you to change your mind about continuing to participate.

Are there benefits to taking part in this research study?
There is no direct benefit to you associated with your participation in the study; however there may be a potential future benefit to society as a whole, from the information obtained from the conduct of this study through the advancement of knowledge.

Will this research study involve the use or disclosure of my identifiable medical record information?
In order to schedule you for the screening visit, we would have reviewed your medical records to see if you are eligible. As part of this research study, some information that we obtain from you will be placed into your medical records held at UPMC, including screening blood tests. This authorization to allow the study team to place research-derived information in to your medical record is valid for an indefinite period of time. We will protect your privacy and the confidentiality of your records, as described in this document, but cannot guarantee the confidentiality of your research records, including information placed in your medical records, once your personal information is disclosed to others outside UPMC or the University. Your private health information will be given to Vitalant and HSCLab staff members in order for your blood to be released and to make sure that the correct blood is given to you on the transfusion visits. Your private information will be given to Vitalant and HSCLab via UPMC secure email with a subject ID. The study personnel will ensure that every effort will be made to keep this information confidential. As an REDS-III RBC-OMICs subject with a SNP, once the study team identifies your genetic data and abnormal red blood cell function, this confirms your eligibility for the main biotin study.

Will my information be kept private?
Any information about you obtained from or for this research study will be kept as confidential (private) as possible. All records related to your involvement in this research study will be kept in a locked file cabinet or in a password protected computer database accessible only to study personnel. Your identity on these records will be indicated by a unique study number, rather than your name, and the information linking this study number with you identity will be kept separate from the research records. You or your family will not be identified in any publication of the research study. Your research information and data may be shared with investigators conducting other research. This information will be de-identifiable. Your stored samples may be shared without identifying you to other researchers who may run additional tests on your samples. These researchers will not be able to identify you from the specimens or from information extracted from your medical record.

Will I be notified of my clinically relevant research results?
You will be notified of any results that may affect your personal health or decisions.

Who will have access to identifiable information related to my participation in this research study?
In addition to the investigators listed on the first page of this authorization (consent) form and their research staff, the following individuals will or may have access to identifiable information (which may include your identifiable medical information) related to your participation in this research study:

- Authorized representatives of the University of Pittsburgh Office of Research Protections may review your identifiable research information (which may include your identifiable medical information) for the purpose of monitoring the appropriate conduct of this research study.

- Authorized representatives of the UPMC hospitals or other affiliated health care

providers may have access to identifiable information (which may include your identifiable medical information) related to your participation in this research study for the purpose of (1) fulfilling orders, made by the investigators, for hospital and health care services (e.g., laboratory tests, diagnostic procedures) associated with research study participation; (2) addressing correct payment for tests and procedures ordered by the investigators; and/or (3) for internal hospital operations (i.e. quality assurance).

- Authorized representatives of this research study (National Institute of Health (NIH) will review and/or obtain identifiable information; which may include the subject's identifiable medical information related to participation in this research study for the purpose of monitoring the accuracy and completeness of the research data and for preparing required scientific analyses of the research data. Authorized representatives of the study sponsors may also be present during the subject's participation in certain research procedures. While the study sponsor understands the importance of maintaining the confidentiality of your identifiable research and medical information, the UPMC and the University of Pittsburgh cannot guarantee the confidentiality of this information after it has been obtained by the study sponsor.

  The Vitalant staff and HSCLab staff will review your identifiable medical information. Vitalant will need your medical information in order for the blood unit to be released from Vitalant to HSCLab and to make sure that HSCLab receives the correct blood unit from Vitalant to biotinylate during the transfusion visits. The HSCLab will need your identifiable medical information in order to release your blood to CTRC and the HSCLab uses your medical information to make sure that HSCLab receives the correct blood unit from Vitalant. Your private information will be given to Vitalant and HSCLab via UPMC secure email with a subject ID. The study personnel will ensure that every effort will be made to keep this information confidential.
- Authorized representatives of the Food and Drug Administration and the study sponsor (the National Heart, Lung, and Blood Institute, a part of the National Institutes of Health), who may need to review the records for accuracy and completeness. Representatives of the study sponsor may also be present during your participation in the research study. While the study sponsor understands the importance of maintaining the confidentiality of your identifiable research and medical record information, UPMC and the University of Pittsburgh cannot guarantee the confidentiality of this information after it has been obtained by the study sponsor. Representatives of the local Vitalant Pittsburgh blood bank will have access to identifiable information and that the blood donation is for participation in this research project.

- If the investigators learn that you or someone with whom you are involved is in serious danger or potential harm, they will need to inform, as required by Pennsylvania law, the appropriate agencies.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not

connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings; if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

Will I have to pay anything to be part of this study?
We will not charge you or your insurance company for any testing procedures, such as the research blood draws, blood draw supplies, etc., that are done during your participation in this research study. All costs of the study are covered by the National Institute of Health (NIH). If you receive a bill or believe that your health insurance has been billed for something that is part of the research study, immediately notify a member of the research team or UPMC Patient Billing Services.

Will I be paid if I take part in this research study?
The total compensation for your participation in the research study is a total of $840.

Visit 1:	$20
Visit 2:	$160
Visit 3:	$200
Visit 4:	$50
Visit 5 :	$40
Visit 6:	$200
Visit 7:	$50
Visit 8 :	$40
Visit 9:	$40
Visit 10:	$40
Total	$840

You will receive the first payment following the completion of Visit 7 and then additional payments after visits 8. 9, and 10. We will also give you a ticket to cover outpatient parking at all visits. In the event you must be withdrawn due to a study-related adverse event, you will be reimbursed for the individual study visits that were completed to date, per the above reimbursement schedule. You will be paid on a reloadable electronic debit card.

If you require a second blood draw visit, we will compensate you $20 and provide parking.

Since you are being compensated for your participation in this study, your name, address, and social security number will be released to the Accounting Office. If the total reimbursement for your participation in research is greater than $600 in a year, this will be reported to the Internal Revenue Service (IRS) as income.

Your biological sample may lead, in the future, to new inventions or products. If the investigators are able to develop new products from the research use of your biological sample, there are currently no plans to share with you any money or other rewards that may result from the development of these new products.

Your data or specimens used in this research study may contribute to a new discovery or treatment. In some instances, these discoveries or treatments may be of commercial value and

may be sold, patented, or licensed by the investigators and the University of Pittsburgh for use in other research or the development of new products. You will not retain any property rights, nor will you share in any money that the investigators, the University of Pittsburgh, or outside agencies may receive.

What happens if I am injured because I took part in this study?
If you believe that you are injured as a result of the research procedures being performed, please contact immediately the Principal Investigator or the study coordinator on the first page of this form. Emergency medical treatment for injuries solely and directly related to your participation in this research study will be provided to you by the hospitals of UPMC. It is possible that UPMC may bill your insurance provider for the costs of this emergency treatment, but none of these costs will be charged directly to you. If your research-related injury requires medical care beyond this emergency treatment, you will be responsible for the costs of this follow-up care unless otherwise specifically stated. There is no plan for monetary compensation. You do not, however, waive any legal rights by signing this form. The University of Pittsburgh researchers and their associates who provide services at UPMC recognize the importance of your voluntary participation in their research studies. These individuals and their staffs will make reasonable efforts to minimize, control, and treat any injuries that may arise as a result of this research.

What are my rights if I take part in this study?
Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits.

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VOLUNTARY CONSENT
The above information has been explained to me and all of my current questions have been answered. I understand that I am encouraged to ask questions about any aspect of this research study during the course of this study, and that such future questions will be answered by a qualified individual or by the investigator(s) listed on the first page of this consent document at the telephone number(s) given. I understand that I may always request that my questions, concerns, or complaints be addressed by a listed investigator.

I understand that I may contact the Human Subjects Protection Advocate of the IRB Office, University of Pittsburgh (1-866-212-2668) to discuss problems, concerns, and questions; obtain information; offer input; or discuss situations that have occurred during my participation.

By signing this form, I consent to participate in this research study and provide my authorization to share my medical records with the research team. A copy of this consent form will be given to me.

_____
Printed Name of Participant

_____ _____
Signature of Participant Date

CERTIFICATION of INFORMED CONSENT
I certify that I have explained the nature and purpose of this research study to the above-named individual(s), and I have discussed the potential benefits and possible risks of study participation. Any questions the individual(s) have about this study have been answered, and we will always be available to address future questions as they arise.

I further certify that no research component of this protocol was begun until after this consent form was signed.

Printed Name of Physician Obtaining Consent | Role in Research Study

Signature of Person Obtaining Consent | Date