- Title: Studies in the Pathogenesis of Systemic Capillary Leak Syndrome
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STUDY TITLE: Studies in the Pathogenesis of Systemic Capillary Leak Syndrome

STUDY SITE: NIH Clinical Center

Cohort: Standard

Consent Version: 31 May 2023

WHO DO YOU CONTACT ABOUT THIS STUDY?

Principal investigator: Dr. Kirk Druey, 301-435-8875, kdruey@niaid.nih.gov

Study coordinator: Robin Eisch, 301-443-1720, robin.eisch@nih.gov

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

You are being asked to take part in a research study at the National Institutes of Health (NIH). Members of the study team will talk with you about the information described in this document. Some people have personal, religious, or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). Take the time needed to ask any questions and discuss this study with NIH staff, and with your family, friends, and personal health care providers. Taking part in research at the NIH is your choice.

If the individual being enrolled is a minor, then the term "you" refers to "you and/or your child" throughout the remainder of this document.

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

IT IS YOUR CHOICE TO TAKE PART IN THE STUDY

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

WHY IS THIS STUDY BEING DONE?

You are invited to participate in this study because you have, or are suspected of having, systemic capillary leak syndrome (SCLS or Clarkson syndrome). The causes of SCLS are unknown, but it is associated with life-threatening drops in blood pressure and leaking of blood

fluids into tissues. SCLS symptoms include runny nose, dizziness, shortness of breath, tightness in the arms and legs, abdominal pain, diarrhea, vomiting, low blood pressure, loss of consciousness, shock, and rarely, death. An episode of SCLS may be mild and resolve on its own, or it may be severe and result in death. Other complications of SCLS include kidney failure (kidneys don't work properly because of damage), breakdown of muscle and/or nerve tissues from the extra fluid collected in the hands and feet, blood clots, and heart failure (heart can't pump enough blood throughout the body), which can occur when the fluid that leaked out of the blood vessels returns back into the bloodstream. Some individuals have ongoing leaking of fluids into tissues leading to swelling but do not experience episodes of low blood pressure.

There is no cure or long-term therapy for SCLS. Individuals who experience episodes of SCLS are treated with fluids given through a vein and drugs such as norepinephrine (adrenaline), which are given to maintain blood pressure. Steroids might also be given; steroids are like the hormones your body makes to fight illnesses and injuries.

This study will try to find possible causes for SCLS, which might lead to better treatments for it in the future.

WHAT WILL HAPPEN DURING THIS STUDY?

You will be asked to provide specific information about your SCLS episodes before your visit at the NIH Clinical Center or remote visit to determine your eligibility to participate in the study. You must have a letter of referral with copies of your medical history records and laboratory studies from your private doctor. Blood samples may also be required ahead of time; the study doctor will let you know if you need to provide blood samples before your study visit.

If you are eligible to participate and can come to the NIH in person, you may be hospitalized at the NIH Clinical Center for 3 to 5 days; you may choose not to be hospitalized. During this visit, you will undergo a physical exam, your medical/medication history will be collected, and the procedures described below will be performed, as necessary. If you are co-enrolled in another NIH protocol, then data that is collected in that study may be shared with and used for research in this study, so that you do not have to repeat these procedures/tests.

Blood draw: A little more than 2 cups of blood may be drawn from a vein in your arm to rule out common causes of low blood pressure, to measure your blood cell counts, to see if your organs are functioning well, including your liver and kidneys, and to evaluate biological and genetic markers of your disease. Your blood will also be tested for the hepatitis B and C virus. Additional tests might be performed on the blood collected from you, as medically indicated.

While in the study, tell the study team if you are participating in other studies or have blood drawn for any other reason.

Genetic testing: Some of the blood drawn from you as part of this study may be used for genetic tests, which will help us better understand the causes of SCLS. Genes determine things like hair and eye color. Genetic tests can help researchers study how health or illness is passed on to you by your parents or from you to your children.

In some cases, we may look for "misspellings" at specific places in your genome previously identified as being associated with SCLS. However, if there are no candidate genes identified to sequence (determine their order), if sequencing of candidate genes does not identify changes

related to your disease, or in cases where it is determined to be the best test, we may use a new type of genetic test called whole exome (genes that code for proteins) or whole genome (entire set of genetic information found in a cell) sequencing on your blood. As part of this test, we will look at every single gene in your genome for changes that could cause or contribute to SCLS. Results from this study will have to be studied in other people with SCLS and their relatives to understand the significance of the results. This research may take years. In addition, you should know that the analyses that we perform in our laboratory are for research purposes only; they may not be as accurate as the tests that are performed in a laboratory that is certified to perform genetic testing or testing for routine clinical care. For these reasons, we will not give you the results of the research tests done on your research samples in most cases. There may be exceptions to what we share with you, and this is described later in this consent form in the section for "Return of research results".

Some of the blood drawn from you may be used to find out your HLA type, which is a genetic test of markers of the immune system. It is usually used to match bone marrow or organ transplants. Determining HLA type is necessary to be able to perform certain research studies; the results of HLA testing will become part of your medical record at the NIH.

Pregnancy test: If you are capable of becoming pregnant, your blood or urine will be tested to see if you are pregnant.

Leukapheresis (apheresis): This procedure will be done by trained staff at the Department of Transfusion Medicine at the NIH Clinical Center on adult patients only. No subject will participate in leukapheresis while pregnant. A pregnancy test will be performed by blood or urine 24 to 48 hours prior to leukapheresis if you are of childbearing potential and must be negative.

You will be asked to sign a separate consent form that will describe in more detail how the procedure will be done and the risks associated with it.

Briefly, blood will be removed through a needle from a vein in your arm, and then your white blood cells, which are cells that help fight infection, will be separated into a machine, and the rest of the blood will be returned to you into a separate vein. A medication used to prevent blood from clotting (citrate) will be added to the blood while in the machine to prevent it from clotting.

The purpose of leukapheresis in this study is to allow the study doctor to obtain a larger number of white blood cells than can be collected by simple blood drawing. Many of our research experiments use more blood than we can get from blood draws. The number of white blood cells collected is a small fraction of the total number in your body. The body quickly replaces the cells that were removed. Similar procedures are used on a daily basis in Blood Banks. The procedure will take approximately 1 to 3 hours.

As part of the procedure, you will have to lie on a recliner or couch. The kits used to collect the leukapheresis products are sterilized, single-use, disposable sets that are not in contact with any person's body fluids other than yours. No blood products are given to you during these procedures. A doctor will be available in or near the leukapheresis clinic at all times.

Bone marrow biopsy and aspiration: Bone marrow biopsy and aspiration may be performed on affected subjects aged 8 through adult. It may be medically indicated or we may do it just for research. You will be asked to sign a separate consent form for this procedure.

The purpose of the bone marrow biopsy and aspiration is to collect a sample of fluid and cells from your bone marrow to determine biological and genetic markers that may contribute to your SCLS; some of the sample may be used for research. The bone marrow aspiration will take about 15 minutes. While you lie on your stomach, the skin over your hip bone will be cleaned with alcohol and iodine, a solution used to disinfect. A numbing medicine will then be injected under the skin into the outer covering of the bone. After the area is numb, a needle will be inserted into the bone. A syringe will be attached to this needle and a fast suction movement will be made. The movement may be repeated several times, so that enough bone marrow cells can be obtained.

After the aspiration, the needle will be removed and either repositioned, or another needle may be used for the biopsy. The biopsy needle will be injected into the bone; the center of the needle will be removed and the hollowed needle will be moved deeper into the bone. This process captures a tiny sample, or core, of bone marrow within the needle; the sample and needle will then be removed, and pressure and a bandage will be applied to the biopsy site.

Clinical digital photography: Pictures may be taken of your skin using different digital cameras on affected subjects aged 8 through adult. You will be asked to sign a standard NIH photography consent form. Although your photographs may be published in medical journals, your identity will not be revealed. The study team will try to protect your identity as much as possible, while providing the information needed to support the research being published. You may decline photographs or add any restrictions you wish on their use. Patches may also be placed on your skin to measure your skin temperature. You may need to wear the patches until the day you are discharged.

Skin testing: If you are at least 16 years old, you may have an allergy skin prick and/or intradermal testing to a group of up to 55 allergens to test for allergies. Skin tests to histamine and morphine may be used as a potential measure of how strongly your endothelial (capillary) cells react when stimulated. Skin testing to allergens and controls involves placing drops of different allergens or controls on the back or arm and then scratching the skin under each drop with a pointed tool. For intradermal testing, a small amount of allergen solution, histamine, or morphine will be injected just under the skin. The skin around the scratch site will develop a small area of itching, redness and/or swelling, similar to a mosquito bite. After 30-60 minutes this will go away. It is important that you do not take antihistamines for 72 hours prior to allergy skin prick testing. Allergy skin testing will not be done if your lung function test shows you have significant asthma. No subject will do skin testing while pregnant. A pregnancy test will be performed on women of childbearing potential by blood or urine 24 to 48 hours prior to skin testing and must be negative.

Skin or tissue biopsies: You may be asked to have skin or tissue biopsies for research purposes. Skin or tissue cells that can be grown and studied in the lab can be useful in understanding systemic capillary leak syndrome and other diseases. Up to 2 biopsies may be taken from the arm, leg, abdomen, back, or other affected area of skin. The biopsy site may be numbed using a spray or cream prior to injecting a local anesthetic. A circular skin biopsy punch will be gently

inserted into the numbed area of the skin and rotated. One to two small 1-5 millimeter each, circles of skin will be removed, and the areas will then be closed using gel foam or steri-strips (a sterile type of band-aid) or by putting in one or two stitches and covering the site with a small dressing. You will be expected to keep the dressing over the biopsy site dry for 1 to 2 days and change the dressing as needed for about a week. If sutures are used, the suture(s) may be removed by your primary care doctor.

If you need a biopsy of other tissue(s) in your body for clinical or diagnostic purposes (for example, colon or liver), then we may use any remaining tissue from that procedure for research purposes. No subject will have a skin biopsy while pregnant. A pregnancy test will be performed on women of childbearing potential by blood or urine 24 to 48 hours prior to skin biopsy and must be negative.

Cardiac MRI: If you are at least 18 years old, then a scan of your heart may be performed, which will take about 45 to 90 minutes. The scan uses a large magnet and radio waves to take pictures of your heart; it does not involve the use of X-rays. The MRI scanner is a large hollow tube. You will lie flat on a table that can slide in and out of the tube. While the scanner takes pictures, you will hear a knocking sound, but you will be fitted with earplugs or earmuffs to dampen the sound. Since the heart moves as you breathe, you will be asked to hold your breath for periods of about 5 to 20 seconds at a time. During part of the scan, you may receive a gadolinium contrasting agent injected into a vein in your arm through a tube called an IV catheter. This contrasting agent brightens the image of the heart or blood vessels. Throughout, your heart rhythm and blood pressure will be monitored. An electrocardiogram (EKG) will be used to monitor your heart rhythm during the procedure. An EKG is a device that measures the normal electrical activity of your heart using wires connected to pads on the skin; the procedure does not cause any pain or harm. A flexible belt may also be used to monitor your breathing. You will be able to communicate with the MRI staff at all times during your scan, and you may ask to be moved out of the machine at any time. No subject will participate in cardiac MRI while pregnant. A pregnancy test will be performed on women of childbearing potential by blood or urine 24 to 48 hours prior to cardiac MRI and must be negative.

Telehealth (Remote) Visits and Send-in Samples: We at NIH understand that it may not be possible or easy for you to travel to NIH. If you are not able to travel to NIH, it is possible to participate in our protocol utilizing telemedicine to conduct remote visits. We can also work with your doctor to obtain samples and have them sent to us. If you cannot travel to NIH, we will:

1. Obtain your medical records from your doctor.
2. Call you after you have had time to review this consent form to discuss the study, answer any questions you may have, and assess if you are ready to sign this consent form either on a paper form or using our telehealth platform. You will then mail back the signed consent to us or it will be electronically signed and entered into your medical record at NIH.
3. Contact you with instructions you will need for a telehealth visit, and conduct the visit remotely. During a telehealth visit, we will talk with you over videoconference to collect your medical/medication history and may also do a brief physical exam as we are able to over the videoconference.

4. Call your doctor with the instructions they need to send us the blood and/or tissue samples.

HOW LONG WILL THE STUDY TAKE?

Your study participation may end 12 months after your first study visit or after your sample is sent to us; during this time, you might be asked to come back to the NIH or have more remote visits as necessary for additional evaluations or if you experience an episode of SCLS. We may work along with your own doctor to make recommendations about your medical care. We may recommend standard medications that have been used in other patients with medical conditions like yours.

You may be asked to collect additional research specimens. This may not require an NIH appointment, as blood samples, for example, could be collected by your local care providers and mailed to the NIH. Someone from the NIH study team may contact you regarding future specimen collection.

HOW MANY PEOPLE WILL PARTICIPATE IN THIS STUDY?

A total of 120 subjects with SCLS and 150 healthy volunteers and relatives of subjects with SCLS are expected to be enrolled in this study.

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

Bone marrow biopsy and aspiration: This procedure is associated with pain and will result in a small bruise. You may feel a mild burning sensation until the numbing medicine starts to work. You will feel a pushing sensation as the needle enters the bone and may experience a sharp pain as the marrow is removed. You will have the pain for a while after the procedure is over. There is also a risk of bleeding during or after the procedure. Bleeding at the biopsy site for more than 2 minutes will be treated with pressure at the site. Infection from the needle puncture is rare, but if this does occur, appropriate treatment will be given. Other problems, which may occur after you leave the NIH, will be managed by your private doctor in consultation with us, if the problem is related to your evaluation.

Cardiac MRI: There are no known long-term risks or consequences of MRI scans. Since you may feel extra warmth from the scanner, please report any sensation of heat during the test. During the scan, it is possible that you may experience something called "peripheral nerve stimulation," which feels like a mild vibration in the skin. If you feel pain from a twitch in the muscle, you should report it to the staff performing the scan. Some individuals may feel claustrophobic while inside the scanner.

The risks of inserting an IV catheter for the gadolinium contrasting agent include bleeding, infection, or inflammation of the skin and vein with pain and swelling.

Mild symptoms from gadolinium infusion occur in fewer than 1% of those who receive it and usually go away quickly. Mild symptoms may include coldness in the arm during the injection, a metallic taste, headache, and nausea. In an extremely small number (fewer than one in 300,000 people) more severe symptoms have been reported including shortness of breath, wheezing, hives, and lowering of blood pressure. You should not receive gadolinium if you previously had an allergic reaction to it. You will be asked about such allergic reactions before gadolinium is given.

People with kidney disease are at risk for a serious reaction to gadolinium contrast called "nephrogenic systemic fibrosis (NSF)". This condition always involves the skin and can also involve the muscles, joints, and internal organs. NSF has resulted in a very small number of deaths. A blood test of your kidney function may be done within the month before an MRI scan with gadolinium contrast. You will not receive gadolinium for a research MRI scan if your kidney function is below the safe level.

Most of the gadolinium contrast leaves the body in the urine. However, the FDA has issued a safety alert that indicates small amounts of gadolinium may remain in the body for months to years. The effects of the retained gadolinium are not clear. At this time, retained gadolinium has not been linked to health risks in people whose kidneys work well. Some types of gadolinium contrast drugs are less likely to remain in the body than others. In this study, we will use the gadolinium contrast drugs that are less likely to remain in the body, whenever possible. We will also give you additional information called a "Medication Guide." Upon request, we will give you individual information about retained gadolinium we see on your studies.

Leukapheresis (apheresis): Donations for this procedure are generally safe and side effects are rare. Pain, bruising, or discomfort at the needle placement site may occur. Sometimes leukapheresis can cause a tingling sensation around the mouth or in the finger, chills, nausea, heartburn, or mild muscle cramps. These side effects can usually be relieved by slowing or temporarily interrupting the leukapheresis or taking a calcium-containing antacid, such as Tums®. Other possible side effects are anxiety, vomiting, and lightheadedness. A temporary drop in your blood pressure may also develop. On rare occasions, infection, fainting, or seizure may occur. Very rarely, a nerve problem at the needle placement site may occur, or malfunction of the machine used for the procedure may occur, resulting in a loss of about one unit (one pint) of your blood. There are possible risks from re-infusion of the blood after being processed by the machine, such as infection or a side effect from the blood components. However, this has not been seen in many thousands of volunteers who have undergone this or similar procedures to date at the NIH. During the leukapheresis procedure, your platelet count may decrease because platelets are collected with the white blood cells. Platelets are cells that help your blood to clot. Taking aspirin in combination with a lowered platelet count may increase your chance of developing bleeding. Therefore, you should not take aspirin or aspirin-containing drugs for 2 weeks after the procedure without physician approval.

Blood draw: The risks associated with drawing blood from a vein in your arm include pain, bruising, hematoma or black and blue mark with a lump caused by the blood being released into the tissues, lightheadedness, fainting, and, rarely, infection at the site. Appropriate treatment may be given for the infection.

Clinical digital photography: Taking pictures of the body may be embarrassing to some people. There is also a rare, but potential risk of skin irritation from the patches. You are invited to talk to us about any concerns you may have related to photography.

Genetic testing: Although your genomic information is unique to you, you share some genomic similarities with your children, parents, brothers, sisters, and other blood relatives. Therefore, learning your research results could mean something about your family members and might cause you or your family distress. Genetic testing can be used to determine if people are directly related. These tests can reveal that a person's biological parents are someone other than their

legal parents. If these facts were previously not known, they could be troubling to learn. In cases where the reported parentage is questioned by the results of the genetic testing, we will not perform further tests to determine the exact genetic relationships, and it is our policy not to discuss such information unless it has direct medical or reproductive implications for you or your family. Before joining the study, it may be beneficial to talk with your family members about whether and how they want you to share your results with them.

Your genetic information is unique to you, however, you do share some genetic information with your children, parents, brothers, sisters, and other blood relatives. Consequently, it may be possible that genetic information from them could be used to help identify you. Similarly, it may be possible that genetic information from you could be used to help identify them. Any genetic information collected or discovered about you or your family will be confidential as described later in this consent form in the section for "Confidentiality Protections Provided in this Study".

Protections against misuse of genetic information

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

Skin testing: Itching, redness and/or swelling, similar to a mosquito bite may occur with skin prick testing. After 30-60 minutes, this will go away.

Skin biopsies: Pain or discomfort may occur during and after a biopsy procedure, even with the use of an anesthetic. There may be mild burning sensation when the numbing medication is injected into the skin. The anesthetic may irritate the skin. Rarely the anesthetic may cause an allergic reaction, which can be treated with medication. There may be bleeding which may require putting pressure on the biopsy site, or other actions to stop the bleeding. Rarely an infection may occur at the site of the biopsy, and may require additional treatment. In certain individuals, the biopsy may heal with a scar or overgrowth of tissue (keloid scar). Overgrowth of tissue or keloid scar formation is more likely to occur if it has happened to you in the past.

What are the risks related to pregnancy?

Some of the procedures done in this study may have increased risks during pregnancy. If you are pregnant or become pregnant while on this study, you may remain on study; however, you will not be asked to complete some components of this protocol while you are pregnant.

WHAT ARE THE BENEFITS OF BEING IN THIS STUDY?

There is no direct benefit from participating in this study. You will, however, be evaluated for your SCLS.

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

Your participation in this study will allow us to learn more about the specific cause(s) of SCLS, which may eventually lead to improved treatment for this disorder.

WHAT OTHER OPTIONS ARE THERE FOR YOU?

Before you decide whether or not to be in this study, we will discuss other options that are available to you. Instead of being in this study, you may choose not to participate and continue to receive care from your private doctor.

DISCUSSION OF FINDINGS

New information about the study

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

Return of research results

This study involves some standard medical tests. We may share the results of medical tests with you and your primary health care provider to help them make decisions about your medical care.

We will also do some research tests and procedures. These are unlikely to tell us anything about your personal health and we will not share research results with you. Rarely, however, research tests could reveal something important about your health. This may include results of genetic testing. If we find a medical condition in our research tests for which you can get treatment, then we will first confirm the results in a clinical lab. This may require getting additional samples from you. We will then share these results with you when they are available. We can counsel you and your healthcare provider about the results.

Genetics is a fast-moving field and new findings for a wide range of diseases are announced every day. By sequencing your entire genome or exome, we may also discover possible "misspellings" in genes not currently recognized as being associated with SCLS. These are called secondary findings. If we discover a secondary finding that might be important to you or your family's health, we plan to tell you about this. However, before we can tell you, we may need to do the test again in another laboratory to be sure that the result is correct. To do so, we may need to ask you to submit another sample for testing. Once these results are available, we will invite you to come to the NIH or schedule a telemedicine visit to learn more about this result and to help you seek follow-up care outside of the NIH if it is needed. The NIH will not generally provide any further follow-up testing or care for this condition for you or your family.

We may not test the samples we have collected from you for several years. Because of this, just because you have not heard from us, you should not assume that you do not have any gene changes that might be important for your health.

We also do not know all the gene changes that cause can cause health problems. We could learn later that some gene changes that now we do not think cause health problems are of concern. We will, however, recheck your genome or exome sequence once in a while as new information related to SCLS becomes available and may report back to you any of our findings. For either

secondary or disease-related findings, you will be given a choice as to whether or not you want to find out about the results. At any point you can tell us that you do not want to us to contact you or tell you about any secondary findings.

We can only provide these results to you. If you want us to tell anyone else, then you must provide us with a signed written release of medical information request.

It is very important for you to keep us updated on how to contact you. If we do not have up to date information, we will not be able to get in touch with you to collect an additional sample or tell you about a secondary finding. If your contact information changes, providing us with the new information is your responsibility. To tell us of your new contact information, you should call or email one of the study contacts listed on the first page of this consent form.

If you have questions or concerns about learning this kind of genetic information, please speak with someone from the study team.

EARLY WITHDRAWAL FROM THE STUDY

You may be removed from this study without your consent for the following reasons:

- The study doctor feels that staying in the study would be harmful to you.
- The study is stopped or cancelled.
- You don't keep your appointments or refuse to undergo study procedures, as required.

STORAGE, SHARING, AND FUTURE RESEARCH USING YOUR SPECIMENS AND DATA

Will your specimens or data be saved by the study team for use in other studies?

As part of this study, we are obtaining specimens and data from you. We plan to store and use these specimens and data for studies other than the one described in this consent form that are going on right now, as well as studies that may be conducted in the future. The specimens and data will be kept in a way that we will still know that they came from you (i.e., they will be identifiable to us). If we use your identifiable specimens or data for future research, our study will be reviewed and approved by an Institutional Review Board who will make sure that we are protecting your confidentiality. These future studies might help us better understand SCLS or other diseases or conditions. This could include studies to develop other research tests, treatments, drugs, or devices, that may lead to the development of a commercial product by the NIH and/or its research or commercial partners. There are no plans to provide financial compensation to you if this happens. Also, it is unlikely that we will learn anything from these studies that may directly benefit you.

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

We may share your specimens and data with other researchers. The other researchers may be doing studies in similar areas to this study or in other unrelated areas. These researchers may be at NIH, other research centers and institutions, or at commercial entities.

One way that we may share your data is by putting it into a large database called a repository, which is a way to make it widely available to the research community. If we do place your data in a repository, it will be labeled with a code (not with your name or other information that could

be used to easily identify you). Even though it will only be labeled with a code, some types of data, in particular data about your genes (called genetic or genomic data), can be used to figure out who you are, although this is difficult to do, and we think it is unlikely to happen.

The data in the repository will be widely available to anyone who wants it.

If we do share your specimens or data, we will know that the specimens and data came from you. However, the other researchers will not know that they came from you (i.e., they will be de-identified).

In addition to the planned use and sharing described above, we might remove any labels from your specimens and data that might identify you (i.e., anonymize them), and use them or share them with other researchers for future studies at the NIH or other places. When we or the other researchers use your anonymized specimens and data for these projects, there will be no way to know that they came from you. We want to make sure that you understand that this is a possibility if you participate in this study. Once we do this, we would not be able to remove your specimens or data from these studies or prevent their use in future studies because we would not be able to tell which specimens or data belong to you.

Risks of storage and sharing of specimens and data

When we store your specimens and data, we take precautions to protect your information from others who should not have access to it. When we share your specimens and data, we will do everything we can to protect your identity, for example, when appropriate, we remove information that can identify you. Even with the safeguards we put in place, we cannot guarantee that your identity will never become known, or that no one will gain unauthorized access to your information. New methods may be created in the future that could make it possible to re-identify your specimens and data.

Can you change your mind about use and sharing for future research?

If you change your mind and do not want us to store and use your specimens and data for future studies, you should contact the study team. We will do our best to comply with your request but cannot guarantee that we will always be able to destroy your specimens and data. For example, if some research with your specimens and data is already complete, the information from that research may still be used. Also, if the specimens and data have been shared already, it might not be possible to withdraw them.

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

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

PAYMENT

Will you receive any type of payment for taking part in this study?

You will be compensated $150 for each leukapheresis procedure you undergo.

You will be paid by check, debit card, direct deposit, or automated clearing house (ACH). If you are unable to finish the study, you will receive compensation for the parts you completed.

With few exceptions, study compensation is considered taxable income that is reportable to the Internal Revenue Service (IRS). A “Form 1099-Other Income” will be sent to you if your total

payments for research participation are $600 or more in a calendar year. If you have unpaid debt to the federal government, please be aware that some or all of your compensation may be automatically reduced to repay that debt on your behalf.

REIMBURSEMENT

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

NIAID will cover some or all of your travel expenses related to participation in this study. This may include direct payments or reimbursements for expenses related to transportation, lodging, and meals. The amount and form of these payments are determined by the NIAID Central Travel Policy for Research Protocol Participants. We will give you a copy of this policy.

If your travel to the NIH Clinical Center (e.g., flight, hotel) is arranged and paid for by the NIH, the agency making the reservations and their representatives will have access to your identifiable information.

To receive payment and/or reimbursement, you may be asked to provide your Social Security number. If you do not provide one, you can still participate in the study, but you may not be able to receive payment and/or reimbursement.

COSTS

Will taking part in this research study cost you anything?

NIH does not bill health insurance companies or participants for any research or related clinical care that you receive at the NIH Clinical Center. We will not pay for your medical care outside of the NIH. The study doctor would be glad to provide telephone consultations to your private doctor upon request during the course of the study. Medical care and medications not directly related to the study must continue to be provided by your private doctor.

CONFLICT OF INTEREST (COI)

The NIH reviews NIH staff researchers at least yearly for conflicts of interest. This process is detailed in a COI Guide. You may ask your research team for a copy of the COI Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines or the guidelines of their home institution, but they do not need to report their personal finances to the NIH.

The NIH and the research team for this study are using a drug developed by PharmAbcine, Inc. through a collaboration between your study team and the company. This drug is only being used for laboratory tests and is not being given to any humans on this study. The company also provides financial support for this study.

CLINICAL TRIAL REGISTRATION AND RESULTS REPORTING

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

CONFIDENTIALITY PROTECTIONS PROVIDED IN THIS STUDY

Will your medical information be kept private?

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

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

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

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

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

Certificate of Confidentiality

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

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

The Certificate does not protect your information when it:

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

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

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

Privacy Act

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

POLICY REGARDING RESEARCH-RELATED INJURIES

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

PROBLEMS OR QUESTIONS

If you have any problems or questions about this study, about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Dr. Kirk Druey, at 301-435-8875 or kdruey@niaid.nih.gov. You may also contact the study coordinator: Robin Eisch, at 301-443-1720 or robin.eisch@nih.gov. You may also call the NIH Clinical Center Patient Representative at 301-496-2626, or the NIH Office of IRB Operations at 301-402-3713, if you have a research-related complaint or concern.

CONSENT DOCUMENT

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

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

Signature of Research Participant	Print Name of Research Participant	Date

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

Signature of LAR	Print Name of LAR	Date

Parent/Guardian of a Minor Participant: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I give permission for my child to take part in this study.

Signature of Parent/Guardian	Print Name of Parent/Guardian	Date
Signature of Parent/Guardian	Print Name of Parent/Guardian	Date

Investigator:

Signature of Investigator	Print Name of Investigator	Date

Witness should sign below if either:

1. **A short form consent process has been used to enroll a non-English speaking subject or**
2. **An oral presentation of the full consent has been used to enroll a blind or illiterate subject**

Signature of Witness	Print Name of Witness	Date

NIH ADMINISTRATIVE SECTION TO BE COMPLETED REGARDING THE USE OF AN INTERPRETER:

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent and served as a witness. The investigator obtaining consent may not also serve as the witness.

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent but did not serve as a witness. The name or ID code of the person providing interpretive support is: _____.

PRINCIPAL INVESTIGATOR: Kirk M Druey, MD

STUDY TITLE: Studies in the Pathogenesis of Systemic Capillary Leak Syndrome

STUDY SITE: NIH Clinical Center

Cohort: Relative

Consent Version: 31 May 2023

WHO DO YOU CONTACT ABOUT THIS STUDY?

Principal investigator: Dr. Kirk Druey, 301-435-8875, kdruey@niaid.nih.gov

Study coordinator: Robin Eisch, 301-443-1720, robin.eisch@nih.gov

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

You are being asked to take part in a research study at the National Institutes of Health (NIH). Members of the study team will talk with you about the information described in this document. Some people have personal, religious, or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). Take the time needed to ask any questions and discuss this study with NIH staff, and with your family, friends, and personal health care providers. Taking part in research at the NIH is your choice.

If the individual being enrolled is a minor, then the term "you" refers to "you and/or your child" throughout the remainder of this document.

IT IS YOUR CHOICE TO TAKE PART IN THE STUDY

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

WHY IS THIS STUDY BEING DONE?

You are invited to participate in this study because your relative has, or is suspected of having, systemic capillary leak syndrome (SCLS or Clarkson syndrome). The causes of SCLS are unknown, but it is associated with life-threatening drops in blood pressure and leaking of blood fluids into tissues. SCLS symptoms include runny nose, dizziness, shortness of breath, tightness in the arms and legs, abdominal pain, diarrhea, vomiting, low blood pressure, loss of consciousness, shock, and rarely, death. An episode of SCLS may be mild and resolve on its own, or it may be severe and result in death. Other complications of SCLS include kidney failure (kidneys don't work properly because of damage), breakdown of muscle and/or nerve tissues from the extra fluid collected in the hands and feet, blood clots, and heart failure (heart can't

pump enough blood throughout the body), which can occur when the fluid that leaked out of the blood vessels return back into the bloodstream. Some individuals have ongoing leaking of fluids into tissues leading to swelling but do not experience episodes of low blood pressure.

There is no cure or long-term therapy for SCLS. Individuals who experience episodes of SCLS are treated with fluids given through a vein and drugs such as norepinephrine (adrenaline), which are given to maintain blood pressure. Steroids might also be given; steroids are like the hormones your body makes to fight illnesses and injuries.

This study will try to find possible causes for SCLS, which might lead to better treatments for it in the future.

WHAT WILL HAPPEN DURING THIS STUDY?

You may or may not be seen at the NIH Clinical Center for the purposes of this study. If you are not seen at the NIH, then mailed-in medical record summaries, blood, will be obtained through your healthcare provider's office after receipt of your signed informed consent form. None of the other procedures described below will be performed if you do not come to the NIH Clinical Center. You may participate in a telehealth visit through the NIH telemedicine system (via videoconference).

Your informed consent will be obtained as outlined below:

- We will send you a copy of the consent form.
- A study team member will review the consent form with you over the phone and will answer any questions you may have.
- You will be asked to provide your name, date of birth, and a verbal consent that you give us permission to test your blood and tissue sample(s).
- You must sign and date the consent form.
- You will then send the signed consent form back to us.
- Once the consent form is received, we may contact you with instructions you will need for a telehealth visit. During a telehealth visit, we will talk with you over videoconference to collect your medical/medication history and may also do a brief physical exam as we are able to over the videoconference.
- We will ask your healthcare provider to provide us with your blood sample(s).

If you are seen at the NIH Clinical Center, your blood will be collected at the NIH. Any or all of the other procedures described below may also be conducted at the NIH. If you are co-enrolled in another NIH protocol, then data that is collected in that study may be shared with and used for research in this study, so that you do not have to repeat these procedures/tests.

Blood draw: About 4 tablespoons of blood may be drawn from a vein in your arm by your healthcare provider or the study doctor at the NIH; the blood may be used to measure your blood cell counts, to see if your organs are functioning well, including your liver and kidneys, and to evaluate biological and genetic markers of SCLS. Your blood may also be tested for the hepatitis B and C virus. While in the study, tell the study team if you are participating in other studies or have blood drawn for any other reason.

Genetic testing: Some of the blood drawn from you as part of this study may be used for genetic tests, which will help us better understand the causes of SCLS. Genes determine things like hair

and eye color. Genetic tests can help researchers study how health or illness is passed on to you by your parents or from you to your children.

In some cases, we may look for "misspellings" at specific places in your genome previously identified as being associated with SCLS. However, if there are no candidate genes identified to sequence (determine their order), if sequencing of candidate genes does not identify changes related to SCLS, or in cases where it is determined to be the best test, we may use a new type of genetic test called whole exome (genes that code for proteins) or whole genome (entire set of genetic information found in a cell) sequencing on your blood. As part of this test, we will look at every single gene in your genome for changes that could cause or contribute to SCLS. Results from this study will have to be studied in people with SCLS and their relatives to understand the significance of the results. This research may take years. In addition, you should know that the analyses that we perform in our laboratory are for research purposes only; they may not be as accurate as the tests that are performed in a laboratory that is certified to perform genetic testing or testing for routine clinical care. For these reasons, we will not give you the results of the research tests done on your research samples in most cases. There may be exceptions to what we share with you, and this is described later in this consent form in the section for "Return of research results".

Some of the blood drawn from you may be used to find out your HLA type, which is a genetic test of markers of the immune system. It is usually used to match bone marrow or organ transplants. Determining HLA type is necessary to be able to perform certain research studies; the results of HLA testing will become part of your medical record at the NIH.

Pregnancy test: If you are capable of becoming pregnant, your blood or urine will be tested to see if you are pregnant.

Leukapheresis (apheresis): This procedure will be done by trained staff at the Department of Transfusion Medicine at the NIH Clinical Center on adult subjects only. No subject will participate in leukapheresis while pregnant. A pregnancy test will be performed by blood or urine 24 to 48 hours prior to leukapheresis if you are of childbearing potential and must be negative.

You will be asked to sign a separate consent form that will describe in more detail how the procedure will be done and the risks associated with it.

Briefly, blood will be removed through a needle from a vein in your arm, and then your white blood cells, which are cells that help fight infection, will be separated into a machine, and the rest of the blood will be returned to you into a separate vein. A medication used to prevent blood from clotting (citrate) will be added to the blood while in the machine to prevent it from clotting.

The purpose of leukapheresis in this study is to allow the study doctor to obtain a larger number of white blood cells than can be collected by simple blood drawing. Many of our research experiments use more blood than we can get from blood draws. The number of white blood cells collected is a small fraction of the total number in your body. The body quickly replaces the cells that were removed. Similar procedures are used on a daily basis in Blood Banks. The procedure will take approximately 1 to 3 hours.

As part of the procedure, you will have to lie on a recliner or couch. The kits used to collect the leukapheresis products are sterilized, single-use, disposable sets that are not in contact with any person's body fluids other than yours. No blood products are given to you during these procedures. A doctor will be available in or near the leukapheresis clinic at all times.

Clinical digital photography: Pictures may be taken of your skin using different digital cameras on adult subjects. You will be asked to sign a standard NIH photography consent form. Although your photographs may be published in medical journals, your identity will not be revealed. The study team will try to protect your identity as much as possible, while providing the information needed to support the research being published. You may decline photographs or add any restrictions you wish on their use. Patches may also be placed on your skin to measure your skin temperature. You may need to wear the patches until the day you are discharged.

Skin Testing: If you are at least 16 years old, you may have allergy skin prick and/or intradermal testing to a group of up to 55 allergens to test for allergies. Skin tests to histamine and morphine may be used as a potential measure of how strongly your endothelial (capillary) cells react when stimulated. Skin testing to allergens and controls involves placing drops of different allergens or controls on the back or arm and then scratching the skin under each drop with a pointed tool. For intradermal testing, a small amount of allergen solution, histamine, or morphine will be injected just under the skin. The skin around the scratch site will develop a small area of itching, redness and/or swelling, similar to a mosquito bite. After 30-60 minutes this will go away. It is important that you do not take antihistamines for 72 hours prior to allergy skin prick testing. Allergy skin testing will not be done if your lung function test shows you have significant asthma. No subject will do skin testing while pregnant. A pregnancy test will be performed on women of childbearing potential by blood or urine 24 to 48 hours prior to skin testing and must be negative.

Skin biopsies: If you are at least 18 years old, you may be asked to have skin biopsies for research purposes. Skin cells that can be grown and studied in the lab can be useful in understanding systemic capillary leak syndrome and other diseases. Up to 2 biopsies may be taken from the arm, leg, abdomen, back, or other area of skin. The biopsy site may be numbed using a spray or cream prior to injecting a local anesthetic. A circular skin biopsy punch will be gently inserted into the numbed area of the skin and rotated. Several small 1-5 millimeter each, circles of skin will be removed, and the area will then be closed using gel foam or steri-strip (a sterile type of band-aid), or by putting in one or two stitches and covering the site with a small dressing. You will be expected to keep the dressing over the biopsy site dry for 1 to 2 days and change the dressing as needed for about a week. If sutures are used, the suture(s) may be removed by your primary care doctor.

No subject will have a skin biopsy while pregnant. A pregnancy test will be performed on women of childbearing potential by blood or urine 24 to 48 hours prior to skin biopsy and must be negative.

Cardiac MRI: If you are at least 18 years old, then a scan of your heart may be performed, which will take about 45 to 90 minutes. The scan uses a large magnet and radio waves to take pictures of your heart; it does not involve the use of X-rays. The MRI scanner is a large hollow tube. You will lie flat on a table that can slide in and out of the tube. While the scanner takes pictures, you will hear a knocking sound, but you will be fitted with earplugs or earmuffs to

dampen the sound. Since the heart moves as you breathe, you will be asked to hold your breath for periods of about 5 to 20 seconds at a time. During part of the scan, you may receive a gadolinium contrasting agent injected into a vein in your arm through a tube called an IV catheter. This contrasting agent brightens the image of the heart or blood vessels. Throughout, your heart rhythm and blood pressure will be monitored. An electrocardiogram (EKG) will be used to monitor your heart rhythm during the procedure. An EKG is a device that measures the normal electrical activity of your heart using wires connected to pads on the skin; the procedure does not cause any pain or harm. A flexible belt may also be used to monitor your breathing. You will be able to communicate with the MRI staff at all times during your scan, and you may ask to be moved out of the machine at any time. No subject will participate in cardiac MRI while pregnant. A pregnancy test will be performed on women of childbearing potential by blood or urine 24 to 48 hours prior to cardiac MRI and must be negative.

Telehealth (Remote) Visits and Send-in Samples: We at NIH understand that it may not be possible or easy for you to travel to NIH. If you are not able to travel to NIH, it is possible to participate in our protocol utilizing telemedicine to conduct remote visits. We can also work with your doctor to obtain samples and have them sent to us. If you cannot travel to NIH, if applicable, we will:

1. Obtain your medical records from your doctor.
2. Call you after you have had time to review this consent form to discuss the study, answer any questions you may have, and assess if you are ready to sign this consent form either on a paper form or using our telehealth platform. You will then mail back the signed consent to us or it will be electronically signed and entered into your medical record at NIH.
3. Contact you with instructions you will need for a telehealth visit and conduct the visit remotely. During a telehealth visit, we will talk with you over videoconference to collect your medical/medication history and may also do a brief physical exam as we are able to over the videoconference.
4. Call your doctor with the instructions they need to send us the blood and/or tissue samples.

HOW LONG WILL THE STUDY TAKE?

Your study participation may end 12 months after you join the study or your blood samples are received at the NIH; during this time, you might be asked to undergo additional evaluations.

You may be asked to collect additional research specimens. This may not require an NIH appointment, as blood samples, for example, could be collected by your local care providers and mailed to the NIH. Someone from the NIH study team may contact you regarding future specimen collection.

HOW MANY PEOPLE WILL PARTICIPATE IN THIS STUDY?

A total of 120 subjects with SCLS and 150 healthy volunteers and relatives of subjects with SCLS are expected to be enrolled in this study.

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

Leukapheresis (apheresis): Donations for this procedure are generally safe and side effects are rare. Pain, bruising, or discomfort at the needle placement site may occur. Sometimes leukapheresis can cause a tingling sensation around the mouth or in the finger, chills, nausea, heartburn, or mild muscle cramps. These side effects can usually be relieved by slowing or temporarily interrupting the leukapheresis or taking a calcium-containing antacid, such as Tums®. Other possible side effects are anxiety, vomiting, and lightheadedness. A temporary drop in your blood pressure may also develop. On rare occasions, infection, fainting, or seizure may occur. Very rarely, a nerve problem at the needle placement site may occur, or malfunction of the machine used for the procedure may occur, resulting in a loss of about one unit (one pint) of your blood. There are possible risks from re-infusion of the blood after being processed by the machine, such as infection or a side effect from the blood components. However, this has not been seen in many thousands of volunteers who have undergone this or similar procedures to date at the NIH. During the leukapheresis procedure, your platelet count may decrease because platelets are collected with the white blood cells. Platelets are cells that help your blood to clot. Taking aspirin in combination with a lowered platelet count may increase your chance of developing bleeding. Therefore, you should not take aspirin or aspirin-containing drugs for 2 weeks after the procedure without physician approval.

Blood draw: The risks associated with drawing blood from a vein in your arm include pain, bruising, hematoma or black and blue mark with a lump caused by the blood being released into the tissues, lightheadedness, fainting, and, rarely, infection at the site. Appropriate treatment may be given for the infection.

Clinical digital photography: Taking pictures of the body may be embarrassing to some people. There is also a rare, but potential risk of skin irritation from the patches. You are invited to talk to us about any concerns you may have related to photography.

Genetic testing: Although your genomic information is unique to you, you share some genomic similarities with your children, parents, brothers, sisters, and other blood relatives. Therefore, learning your research results could mean something about your family members and might cause you or your family distress. Genetic testing can be used to determine if people are directly related. These tests can reveal that a person's biological parents are someone other than their legal parents. If these facts were previously not known, they could be troubling to learn. In cases where the reported parentage is questioned by the results of the genetic testing, we will not perform further tests to determine the exact genetic relationships, and it is our policy not to discuss such information unless it has direct medical or reproductive implications for you or your family. Before joining the study, it may be beneficial to talk with your family members about whether and how they want you to share your results with them.

Your genetic information is unique to you, however, you do share some genetic information with your children, parents, brothers, sisters, and other blood relatives. Consequently, it may be possible that genetic information from them could be used to help identify you. Similarly, it may be possible that genetic information from you could be used to help identify them. Any genetic information collected or discovered about you or your family will be confidential as described later in this consent form in the section for "Confidentiality Protections Provided in this Study".

Protections against misuse of genetic information

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

Skin testing: Itching, redness and/or swelling, similar to a mosquito bite may occur with skin prick testing. After 30-60 minutes, this will go away.

Skin biopsies: Pain or discomfort may occur during and after a biopsy procedure, even with the use of an anesthetic. There may be mild burning sensation when the numbing medication is injected into the skin. The anesthetic may irritate the skin. Rarely the anesthetic may cause an allergic reaction, which can be treated with medication. There may be bleeding which may require putting pressure on the biopsy site, or other actions to stop the bleeding. Rarely an infection may occur at the site of the biopsy, and may require additional treatment. In certain individuals, the biopsy may heal with a scar or overgrowth of tissue (keloid scar). Overgrowth of tissue or keloid scar formation is more likely to occur if it has happened to you in the past. Additional medications, treatments, or procedures related to the biopsy may be implemented at the discretion of your healthcare provider.

Cardiac MRI: There are no known long-term risks or consequences of MRI scans. Since you may feel extra warmth from the scanner, please report any sensation of heat during the test. During the scan, it is possible that you may experience something called "peripheral nerve stimulation," which feels like a mild vibration in the skin. If you feel pain from a twitch in the muscle, you should report it to the staff performing the scan. Some individuals may feel claustrophobic while inside the scanner.

The risks of inserting an IV catheter for the gadolinium contrasting agent include bleeding, infection, or inflammation of the skin and vein with pain and swelling.

Mild symptoms from gadolinium infusion occur in fewer than 1% of those who receive it and usually go away quickly. Mild symptoms may include coldness in the arm during the injection, a metallic taste, headache, and nausea. In an extremely small number (fewer than one in 300,000 people) more severe symptoms have been reported including shortness of breath, wheezing, hives, and lowering of blood pressure. You should not receive gadolinium if you previously had an allergic reaction to it. You will be asked about such allergic reactions before gadolinium is given.

People with kidney disease are at risk for a serious reaction to gadolinium contrast called “nephrogenic systemic fibrosis (NSF)”. This condition always involves the skin and can also involve the muscles, joints, and internal organs. NSF has resulted in a very small number of deaths. A blood test of your kidney function may be done within the month before an MRI scan with gadolinium contrast. You will not receive gadolinium for a research MRI scan if your kidney function is below the safe level.

Most of the gadolinium contrast leaves the body in the urine. However, the FDA has issued a safety alert that indicates small amounts of gadolinium may remain in the body for months to years. The effects of the retained gadolinium are not clear. At this time, retained gadolinium has not been linked to health risks in people whose kidneys work well. Some types of gadolinium contrast drugs are less likely to remain in the body than others. In this study, we will use the gadolinium contrast drugs that are less likely to remain in the body, whenever possible. We will also give you additional information called a "Medication Guide." Upon request, we will give you individual information about retained gadolinium we see on your study.

What are the risks related to pregnancy?

Some of the procedures done in this study may have increased risks during pregnancy. If you are pregnant or become pregnant while on this study, you may remain on study, however, you will not be asked to complete some components of this protocol while you are pregnant.

WHAT ARE THE BENEFITS OF BEING IN THIS STUDY?

There is no direct benefit from participating in this study.

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

Your participation will allow us to learn more about the specific cause(s) of SCLS, which may eventually lead to improved treatment for this disorder.

WHAT OTHER OPTIONS ARE THERE FOR YOU?

You may choose not to participate in this study.

DISCUSSION OF FINDINGS

New information about the study

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

Return of research results

This study involves some standard medical tests. We may share the results of medical tests with you and your primary health care provider to help them make decisions about your medical care.

We will also do some research tests and procedures. These are unlikely to tell us anything about your personal health and we will not share research results with you. Rarely, however, research tests could reveal something important about your health. This may include results of genetic testing. If we find a medical condition in our research tests for which you can get treatment, then we will first confirm the results in a clinical lab. This may require getting additional samples from you. We will then share these results with you when they are available. We can counsel you and your healthcare provider about the results.

Genetics is a fast-moving field and new findings for a wide range of diseases are announced every day. By sequencing your entire genome or exome, we may also discover possible "misspellings" in genes not currently recognized as being associated with SCLS. These are

called secondary findings. If we discover a secondary finding that might be important to you or your family's health, we plan to tell you about this. However, before we can tell you, we may need to do the test again in another laboratory to be sure that the result is correct. To do so, we may need to ask you to submit another sample for testing. Once these results are available, we will invite you to come to the NIH or schedule a telemedicine visit to learn more about this result and to help you seek follow-up care outside of the NIH if it is needed. The NIH will not generally provide any further follow-up testing or care for this condition for you or your family.

We may not test the samples we have collected from you for several years. Because of this, just because you have not heard from us, you should not assume that you do not have any gene changes that might be important for your health.

We also do not know all the gene changes that cause can cause health problems. We could learn later that some gene changes that now we do not think cause health problems are of concern. We will, however, recheck your genome or exome sequence once in a while as new information related to SCLS becomes available and may report back to you any of our findings. For either secondary or disease-related findings, you will be given a choice as to whether or not you want to find out about the results. At any point you can tell us that you do not want to us to contact you or tell you about any secondary findings.

We can only provide these results to you. If you want us to tell anyone else, then you must provide us with a signed written release of medical information request.

It is very important for you to keep us updated on how to contact you. If we do not have up to date information, we will not be able to get in touch with you to collect an additional sample or tell you about a secondary finding. If your contact information changes, providing us with the new information is your responsibility. To tell us of your new contact information, you should call or email one of the study contacts listed on the first page of this consent form.

If you have questions or concerns about learning this kind of genetic information, please speak with someone from the study team.

EARLY WITHDRAWAL FROM THE STUDY

You may be removed from this study without your consent for the following reasons:

- The study is stopped or cancelled.
- You refuse to undergo study procedures, as required.

STORAGE, SHARING, AND FUTURE RESEARCH USING YOUR SPECIMENS AND DATA

Will your specimens or data be saved by the study team for use in other studies?

As part of this study, we are obtaining specimens and data from you. We plan to store and use these specimens and data for studies other than the one described in this consent form that are going on right now, as well as studies that may be conducted in the future. The specimens and data will be kept in a way that we will still know that they came from you (i.e., they will be identifiable to us). If we use your identifiable specimens or data for future research, our study will be reviewed and approved by an Institutional Review Board who will make sure that we are protecting your confidentiality. These future studies might help us better understand SCLS or

other diseases or conditions. This could include studies to develop other research tests, treatments, drugs, or devices, that may lead to the development of a commercial product by the NIH and/or its research or commercial partners. There are no plans to provide financial compensation to you if this happens. Also, it is unlikely that we will learn anything from these studies that may directly benefit you.

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

We may share your specimens and data with other researchers. The other researchers may be doing studies in similar areas to this study or in other unrelated areas. These researchers may be at NIH, other research centers and institutions, or at commercial entities.

One way that we may share your data is by putting it into a large database called a repository, which is a way to make it widely available to the research community. If we do place your data in a repository, it will be labeled with a code (not with your name or other information that could be used to easily identify you). Even though it will only be labeled with a code, some types of data, in particular data about your genes (called genetic or genomic data), can be used to figure out who you are, although this is difficult to do, and we think it is unlikely to happen.

The data in the repository will be widely available to anyone who wants it.

If we do share your specimens or data, we will know that the specimens and data came from you. However, the other researchers will not know that they came from you (i.e., they will be de-identified).

In addition to the planned use and sharing described above, we might remove any labels from your specimens and data that might identify you (i.e., anonymize them), and use them or share them with other researchers for future studies at the NIH or other places. When we or the other researchers use your anonymized specimens and data for these projects, there will be no way to know that they came from you. We want to make sure that you understand that this is a possibility if you participate in this study. Once we do this, we would not be able to remove your specimens or data from these studies or prevent their use in future studies because we would not be able to tell which specimens or data belong to you.

Risks of storage and sharing of specimens and data

When we store your specimens and data, we take precautions to protect your information from others who should not have access to it. When we share your specimens and data, we will do everything we can to protect your identity, for example, when appropriate, we remove information that can identify you. Even with the safeguards we put in place, we cannot guarantee that your identity will never become known, or that no one will gain unauthorized access to your information. New methods may be created in the future that could make it possible to re-identify your specimens and data.

Can you change your mind about use and sharing for future research?

If you change your mind and do not want us to store and use your specimens and data for future studies, you should contact the study team. We will do our best to comply with your request but cannot guarantee that we will always be able to destroy your specimens and data. For example, if some research with your specimens and data is already complete, the information from that

research may still be used. Also, if the specimens and data have been shared already, it might not be possible to withdraw them.

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

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

PAYMENT

Will you receive any type of payment for taking part in this study?

You will be compensated $150 for each leukapheresis procedure you undergo.

You will be paid by check, debit card, direct deposit, or automated clearing house (ACH). If you are unable to finish the study, you will receive compensation for the parts you completed.

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

REIMBURSEMENT

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

NIAID will cover some or all of your travel expenses related to participation in this study. This may include direct payments or reimbursements for expenses related to transportation, lodging, and meals. The amount and form of these payments are determined by the NIAID Central Travel Policy for Research Protocol Participants. We will give you a copy of this policy.

If your travel to the NIH Clinical Center (e.g., flight, hotel) is arranged and paid for by the NIH, the agency making the reservations and their representatives will have access to your identifiable information.

To receive payment and/or reimbursement, you may be asked to provide your Social Security number. If you do not provide one, you can still participate in the study, but you may not be able to receive payment and/or reimbursement.

COSTS

Will taking part in this research study cost you anything?

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

CONFLICT OF INTEREST (COI)

The NIH reviews NIH staff researchers at least yearly for conflicts of interest. This process is detailed in a COI Guide. You may ask your research team for a copy of the COI Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines or the guidelines of their home institution, but they do not need to report their personal finances to the NIH.

The NIH and the research team for this study are using a drug developed by PharmAbcine, Inc. through a collaboration between your study team and the company. This drug is only being used for laboratory tests and is not being given to any humans on this study. The company also provides financial support for this study.

CLINICAL TRIAL REGISTRATION AND RESULTS REPORTING

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

CONFIDENTIALITY PROTECTIONS PROVIDED IN THIS STUDY

Will your medical information be kept private?

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

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

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

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

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

Certificate of Confidentiality

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

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

The Certificate does not protect your information when it:

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

3. is for other research;
4. is disclosed with your consent.

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

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

Privacy Act

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

POLICY REGARDING RESEARCH-RELATED INJURIES

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

PROBLEMS OR QUESTIONS

If you have any problems or questions about this study, about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Dr. Kirk Druey, at 301-435-8875 or kdruey@niaid.nih.gov. You may also contact the study coordinator: Robin Eisch, at 301-443-1720 or robin.eisch@nih.gov. You may also call the NIH Clinical Center Patient Representative at 301-496-2626, or the NIH Office of IRB Operations at 301-402-3713, if you have a research-related complaint or concern.

CONSENT DOCUMENT

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

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

Signature of Research Participant	Print Name of Research Participant	Date

Parent/Guardian of a Minor Participant: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I give permission for my child to take part in this study.

Signature of Parent/Guardian	Print Name of Parent/Guardian	Date
Signature of Parent/Guardian	Print Name of Parent/Guardian	Date

Investigator:

Signature of Investigator	Print Name of Investigator	Date

Witness should sign below if either:

1. **A short form consent process has been used to enroll a non-English speaking subject or**
2. **An oral presentation of the full consent has been used to enroll a blind or illiterate subject**

Signature of Witness	Print Name of Witness	Date

NIH ADMINISTRATIVE SECTION TO BE COMPLETED REGARDING THE USE OF AN INTERPRETER:

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent and served as a witness. The investigator obtaining consent may not also serve as the witness.

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent but did not serve as a witness. The name or ID code of the person providing interpretive support is: _____.

PRINCIPAL INVESTIGATOR: Kirk M Druey, MD

STUDY TITLE: Studies in the Pathogenesis of Systemic Capillary Leak Syndrome

STUDY SITE: NIH Clinical Center

Cohort: Healthy Volunteer

Consent Version: 31 May 2023

WHO DO YOU CONTACT ABOUT THIS STUDY?

Principal investigator: Dr. Kirk Druey, 301-435-8875, kdruey@niaid.nih.gov

Study coordinator: Robin Eisch, 301-443-1720, robin.eisch@nih.gov

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

You are being asked to take part in a research study at the National Institutes of Health (NIH). Members of the study team will talk with you about the information described in this document. Some people have personal, religious, or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). Take the time needed to ask any questions and discuss this study with NIH staff, and with your family, friends, and personal health care providers. Taking part in research at the NIH is your choice.

IT IS YOUR CHOICE TO TAKE PART IN THE STUDY

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

WHY IS THIS STUDY BEING DONE?

You are invited to participate in this study because you have indicated that you are a healthy adult who can provide blood, tissue, MRI, leukapheresis and/or skin testing procedures and clinical digital photographs for research purposes. Your participation will help improve our understanding of the systemic capillary leak syndrome (SCLS or Clarkson syndrome). The causes of SCLS are unknown, but it is associated with life-threatening drops in blood pressure and leaking of blood fluids into tissues. SCLS symptoms include runny nose, dizziness, shortness of breath, tightness in the arms and legs, abdominal pain, diarrhea, vomiting, low blood pressure, loss of consciousness, shock, and rarely, death. An episode of SCLS may be mild and resolve on its own, or it may be severe and result in death. Other complications of SCLS include kidney failure (kidneys don't work properly because of damage), breakdown of muscle and/or nerve tissues from the extra fluid collected in the hands and feet, blood clots, and heart failure (heart

can't pump enough blood throughout the body), which can occur when the fluid that leaked out of the blood vessels returns back into the bloodstream. Some individuals have ongoing leaking of fluids into tissues leading to swelling but do not experience episodes of low blood pressure.

There is no cure or long-term therapy for SCLS. Individuals who experience episodes of SCLS are treated with fluids given through a vein and drugs such as norepinephrine (adrenaline), which are given to maintain blood pressure. Steroids might also be given; steroids are like the hormones your body makes to fight illnesses and injuries.

This study will try to find possible causes for SCLS, which might lead to better treatments for it in the future.

WHAT WILL HAPPEN DURING THIS STUDY?

If you join this study, you will be asked to attend study visits at the NIH Clinical Center. You may participate in a telehealth visit through the NIH telemedicine system (via videoconference). During a telehealth visit, we will talk with you over videoconference to collect your medical/medication history and may also do a brief physical exam as we are able to over the videoconference. If your visit is at the NIH Clinical Center, your blood will be collected, and you may have any or all of the other procedures described below. If you are co-enrolled in another NIH protocol, then data that is collected in that study may be shared with and used for research in this study, so that you do not have to repeat these procedures/tests.

Blood draw: About ¾ cup of blood may be drawn from a vein in your arm by your healthcare provider or the study doctor at the NIH; the blood may be used to measure your blood cell counts, to see if your organs are functioning well, including your liver and kidneys, and to evaluate biological and genetic markers of SCLS. Your blood may also be tested for the hepatitis B and C virus. Additional tests might be performed on the blood collected from you, as medically indicated. While in the study, tell the study team if you are participating in other studies or have blood drawn for any other reason.

Genetic testing: Some of the blood drawn from you as part of this study may be used for genetic tests, which will help us better understand the causes of SCLS. Genes determine things like hair and eye color. Genetic tests can help researchers study how health or illness is passed on to you by your parents or from you to your children.

In some cases, we may look for "misspellings" at specific places in your genome previously identified as being associated with SCLS. However, if there are no candidate genes identified to sequence (determine their order), if sequencing of candidate genes does not identify changes related to SCLS, or in cases where it is determined to be the best test, we may use a new type of genetic test called whole exome (genes that code for proteins) or whole genome (entire set of genetic information found in a cell) sequencing on your blood. As part of this test, we will look at every single gene in your genome for changes that could cause or contribute to SCLS. Results from this study will have to be studied in people with SCLS and their relatives to understand the significance of the results. This research may take years. In addition, you should know that the analyses that we perform in our laboratory are for research purposes only; they may not be as accurate as the tests that are performed in a laboratory that is certified to perform genetic testing or testing for routine clinical care. For these reasons, we will not give you the results of the research tests done on your research samples in most cases. There may be exceptions to what we

share with you, and this is described later in this consent form in the section for "Return of research results".

Some of the blood drawn from you may be used to find out your HLA type, which is a genetic test of markers of the immune system. It is usually used to match bone marrow or organ transplants. Determining HLA type is necessary to be able to perform certain research studies; the results of HLA testing will become part of your medical record at the NIH.

Pregnancy test: If you are capable of becoming pregnant, your blood or urine will be tested to see if you are pregnant. If you are pregnant, you cannot participate in this study.

Clinical digital photography: Pictures may be taken of your skin using different digital cameras. You will be asked to sign a standard NIH photography consent form. Although your photographs may be published in medical journals, your identity will not be revealed. The study team will try to protect your identity as much as possible, while providing the information needed to support the research being published. You may decline photographs or add any restrictions you wish on their use.

Skin testing: You may have allergy skin prick and/or intradermal testing to a group of up to 55 allergens to test for allergies. Skin tests to histamine and morphine may be used as a potential measure of how strongly your endothelial (capillary) cells react when stimulated. Skin testing to allergens and controls involves placing drops of different allergens or controls on the back or arm and then scratching the skin under each drop with a pointed tool. For intradermal testing, a small amount of allergen solution, histamine, or morphine will be injected just under the skin. The skin around the scratch site will develop a small area of itching, redness and/or swelling, similar to a mosquito bite. After 30-60 minutes this will go away. It is important that you do not take antihistamines for 72 hours prior to allergy skin prick testing. Allergy skin testing will not be done if your lung function test shows you have significant asthma. No subject will do skin testing while pregnant. A pregnancy test will be performed on women of childbearing potential by blood or urine 24 to 48 hours prior to skin testing and must be negative.

Skin biopsies: You may be asked to have skin biopsy for research purposes. Skin cells that can be grown and studied in the lab can be useful in understanding systemic capillary leak syndrome and other diseases. Up to 2 biopsies may be taken from the arm, leg, abdomen, back, or other area of skin. The biopsy sites may be numbed using a spray or cream prior to injecting a local anesthetic. A circular skin biopsy punch will be gently inserted into the numbed area of the skin and rotated. One to two small 1-5 millimeter each, circles of skin will be removed and the areas will then be closed using gel foam or steri-strips (a sterile type of band-aid), or by putting in one or two stitches and covering the site with a small dressing. You will be expected to keep the dressing over the biopsy site dry for 1 to 2 days and change the dressing as needed for about a week. If sutures are used, the suture(s) may be removed by your primary care doctor. A pregnancy test will be performed on women of childbearing potential by blood or urine 24 to 48 hours prior to skin testing and skin biopsy and must be negative.

Cardiac MRI: We will perform a scan of your heart, which will take about 45 to 90 minutes. The scan uses a large magnet and radio waves to take pictures of your heart; it does not involve the use of X-rays. The MRI scanner is a large hollow tube. You will lie flat on a table that can slide in and out of the tube. While the scanner takes pictures, you will hear a knocking sound, but

you will be fitted with earplugs or earmuffs to dampen the sound. Since the heart moves as you breathe, you will be asked to hold your breath for periods of about 5 to 20 seconds at a time. During part of the scan, you may receive a gadolinium contrasting agent injected into a vein in your arm through a tube called an IV catheter. This contrasting agent brightens the image of the heart or blood vessels. Throughout, your heart rhythm and blood pressure will be monitored. An electrocardiogram (EKG) will be used to monitor your heart rhythm during the procedure. An EKG is a device that measures the normal electrical activity of your heart using wires connected to pads on the skin; the procedure does not cause any pain or harm. A flexible belt may also be used to monitor your breathing. You will be able to communicate with the MRI staff at all times during your scan, and you may ask to be moved out of the machine at any time. No subject will participate in cardiac MRI while pregnant. A pregnancy test will be performed on women of childbearing potential by blood or urine 24 to 48 hours prior to cardiac MRI and must be negative.

Leukapheresis (apheresis): This procedure will be done by trained staff at the Department of Transfusion Medicine at the NIH Clinical Center on adult patients only. No subject will participate in leukapheresis while pregnant. A pregnancy test will be performed by blood or urine 24 to 48 hours prior to leukapheresis if you are of childbearing potential and must be negative.

You will be asked to sign a separate consent form that will describe in more detail how the procedure will be done and the risks associated with it.

Briefly, blood will be removed through a needle from a vein in your arm, and then your white blood cells, which are cells that help fight infection, will be separated into a machine, and the rest of the blood will be returned to you into a separate vein. A medication used to prevent blood from clotting (citrate) will be added to the blood while in the machine to prevent it from clotting.

The purpose of leukapheresis in this study is to allow the study doctor to obtain a larger number of white blood cells than can be collected by simple blood drawing. Many of our research experiments use more blood than we can get from blood draws. The number of white blood cells collected is a small fraction of the total number in your body. The body quickly replaces the cells that were removed. Similar procedures are used on a daily basis in Blood Banks. The procedure will take approximately 1 to 3 hours.

As part of the procedure, you will have to lie on a recliner or couch. The kits used to collect the leukapheresis products are sterilized, single-use, disposable sets that are not in contact with any person's body fluids other than yours. No blood products are given to you during these procedures. A doctor will be available in or near the leukapheresis clinic at all times.

HOW LONG WILL THE STUDY TAKE?

Your study participation may end 12 months after your first visit at the NIH; during this time, you might be asked to come back to the NIH as necessary for additional evaluations.

You may be asked to collect additional research specimens. This may not require an additional NIH appointment, as blood samples, for example, could be collected by your local care providers and mailed to the NIH. Someone from the NIH study team may contact you regarding future specimen collection.

HOW MANY PEOPLE WILL PARTICIPATE IN THIS STUDY?

A total of 120 subjects with SCLS and 150 healthy volunteers and relatives of subjects with SCLS are expected to be enrolled in this study.

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

Blood draw: The risks associated with drawing blood from a vein in your arm include pain, bruising, hematoma or black and blue mark with a lump caused by the blood being released into the tissues, lightheadedness, fainting, and, rarely, infection at the site. Appropriate treatment may be given for the infection.

Genetic testing: Although your genomic information is unique to you, you share some genomic similarities with your children, parents, brothers, sisters, and other blood relatives. Therefore, learning your research results could mean something about your family members and might cause you or your family distress. Genetic testing can be used to determine if people are directly related. These tests can reveal that a person's biological parents are someone other than their legal parents. If these facts were previously not known, they could be troubling to learn. In cases where the reported parentage is questioned by the results of the genetic testing, we will not perform further tests to determine the exact genetic relationships, and it is our policy not to discuss such information unless it has direct medical or reproductive implications for you or your family. Before joining the study, it may be beneficial to talk with your family members about whether and how they want you to share your results with them.

Your genetic information is unique to you, however, you do share some genetic information with your children, parents, brothers, sisters, and other blood relatives. Consequently, it may be possible that genetic information from them could be used to help identify you. Similarly, it may be possible that genetic information from you could be used to help identify them. Any genetic information collected or discovered about you or your family will be confidential as described later in this consent form in the section for "Confidentiality Protections Provided in this Study".

Protections against misuse of genetic information

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

Clinical digital photography: Taking pictures of the body may be embarrassing to some people. There is also a rare, but potential risk of skin irritation from the patches. You are invited to talk to your healthcare provider or to us about any concerns you may have related to photography.

Skin biopsies: Pain or discomfort may occur during and after a biopsy procedure, even with the use of an anesthetic. There may be mild burning sensation when the numbing medication is injected into the skin. The anesthetic may irritate the skin. Rarely the anesthetic may cause an allergic reaction, which can be treated with medication. There may be bleeding which may

require putting pressure on the biopsy site, or other actions to stop the bleeding. Rarely an infection may occur at the site of the biopsy, and may require additional treatment. In certain individuals, the biopsy may heal with a scar or overgrowth of tissue (keloid scar). Overgrowth of tissue or keloid scar formation is more likely to occur if it has happened to you in the past.

Cardiac MRI: There are no known long-term risks or consequences of MRI scans. Since you may feel extra warmth from the scanner, please report any sensation of heat during the test. During the scan, it is possible that you may experience something called "peripheral nerve stimulation," which feels like a mild vibration in the skin. If you feel pain from a twitch in the muscle, you should report it to the staff performing the scan. Some individuals may feel claustrophobic while inside the scanner.

The risks of inserting an IV catheter for the gadolinium contrasting agent include bleeding, infection, or inflammation of the skin and vein with pain and swelling.

Mild symptoms from gadolinium infusion occur in fewer than 1% of those who receive it and usually go away quickly. Mild symptoms may include coldness in the arm during the injection, a metallic taste, headache, and nausea. In an extremely small number (fewer than one in 300,000 people) more severe symptoms have been reported including shortness of breath, wheezing, hives, and lowering of blood pressure. You should not receive gadolinium if you previously had an allergic reaction to it. You will be asked about such allergic reactions before gadolinium is given.

People with kidney disease are at risk for a serious reaction to gadolinium contrast called “nephrogenic systemic fibrosis (NSF)”. This condition always involves the skin and can also involve the muscles, joints, and internal organs. NSF has resulted in a very small number of deaths. A blood test of your kidney function may be done within the month before an MRI scan with gadolinium contrast. You will not receive gadolinium for a research MRI scan if your kidney function is below the safe level.

Most of the gadolinium contrast leaves the body in the urine. However, the FDA has issued a safety alert that indicates small amounts of gadolinium may remain in the body for months to years. The effects of the retained gadolinium are not clear. At this time, retained gadolinium has not been linked to health risks in people whose kidneys work well. Some types of gadolinium contrast drugs are less likely to remain in the body than others. In this study, we will use the gadolinium contrast drugs that are less likely to remain in the body, whenever possible. We will also give you additional information called a “Medication Guide.” Upon request, we will give you individual information about retained gadolinium we see on your study.

Leukapheresis (apheresis): Donations for this procedure are generally safe and side effects are rare. Pain, bruising, or discomfort at the needle placement site may occur. Sometimes leukapheresis can cause a tingling sensation around the mouth or in the finger, chills, nausea, heartburn, or mild muscle cramps. These side effects can usually be relieved by slowing or temporarily interrupting the leukapheresis or taking a calcium-containing antacid, such as Tums®. Other possible side effects are anxiety, vomiting, and lightheadedness. A temporary drop in your blood pressure may also develop. On rare occasions, infection, fainting, or seizure may occur. Very rarely, a nerve problem at the needle placement site may occur, or malfunction of the machine used for the procedure may occur, resulting in a loss of about one unit (one pint)

of your blood. There are possible risks from re-infusion of the blood after being processed by the machine, such as infection or a side effect from the blood components. However, this has not been seen in many thousands of volunteers who have undergone this or similar procedures to date at the NIH. During the leukapheresis procedure, your platelet count may decrease because platelets are collected with the white blood cells. Platelets are cells that help your blood to clot. Taking aspirin in combination with a lowered platelet count may increase your chance of developing bleeding. Therefore, you should not take aspirin or aspirin-containing drugs for 2 weeks after the procedure without physician approval.

What are the risks related to pregnancy?

Some of the procedures done in this study may have increased risks during pregnancy. Therefore, healthy volunteers may not be pregnant. If you become pregnant while on study, we ask you to inform us, and you will be removed from the study.

WHAT ARE THE BENEFITS OF BEING IN THIS STUDY?

There is no direct benefit from participating in this study.

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

Your participation will allow us to learn more about the specific cause(s) of SCLS, which may eventually lead to improved treatment for this disorder.

WHAT OTHER OPTIONS ARE THERE FOR YOU?

You may choose not to participate in this study.

DISCUSSION OF FINDINGS

New information about the study

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

Return of research results

This study involves some standard medical tests. We may share the results of medical tests with you and your primary health care provider to help them make decisions about your medical care.

We will also do some research tests and procedures. These are unlikely to tell us anything about your personal health and we will not share research results with you. Rarely, however, research tests could reveal something important about your health. This may include results of genetic testing. If we find a medical condition in our research tests for which you can get treatment, then we will first confirm the results in a clinical lab. This may require getting additional samples from you. We will then share these results with you when they are available. We can counsel you and your healthcare provider about the results.

Genetics is a fast-moving field and new findings for a wide range of diseases are announced every day. By sequencing your entire genome or exome, we may also discover possible "misspellings" in genes not currently recognized as being associated with SCLS. These are

called secondary findings. If we discover a secondary finding that might be important to you or your family's health, we plan to tell you about this. However, before we can tell you, we may need to do the test again in another laboratory to be sure that the result is correct. To do so, we may need to ask you to submit another sample for testing. Once these results are available, we will invite you to come to the NIH or schedule a telemedicine visit to learn more about this result and to help you seek follow-up care outside of the NIH if it is needed. The NIH will not generally provide any further follow-up testing or care for this condition for you or your family.

We may not test the samples we have collected from you for several years. Because of this, just because you have not heard from us, you should not assume that you do not have any gene changes that might be important for your health.

We also do not know all the gene changes that cause can cause health problems. We could learn later that some gene changes that now we do not think cause health problems are of concern. We will, however, recheck your genome or exome sequence once in a while as new information related to SCLS becomes available and may report back to you any of our findings. For either secondary or disease-related findings, you will be given a choice as to whether or not you want to find out about the results. At any point you can tell us that you do not want to us to contact you or tell you about any secondary findings.

We can only provide these results to you. If you want us to tell anyone else, then you must provide us with a signed written release of medical information request.

It is very important for you to keep us updated on how to contact you. If we do not have up to date information, we will not be able to get in touch with you to collect an additional sample or tell you about a secondary finding. If your contact information changes, providing us with the new information is your responsibility. To tell us of your new contact information, you should call or email one of the study contacts listed on the first page of this consent form.

If you have questions or concerns about learning this kind of genetic information, please speak with someone from the study team.

EARLY WITHDRAWAL FROM THE STUDY

You may be removed from this study without your consent for the following reasons:

- The study is stopped or cancelled.
- You become pregnant.
- You don't keep your appointments or refuse to undergo study procedures, as required.

STORAGE, SHARING, AND FUTURE RESEARCH USING YOUR SPECIMENS AND DATA

Will your specimens or data be saved by the study team for use in other studies?

As part of this study, we are obtaining specimens and data from you. We plan to store and use these specimens and data for studies other than the one described in this consent form that are going on right now, as well as studies that may be conducted in the future. The specimens and data will be kept in a way that we will still know that they came from you (i.e., they will be identifiable to us). If we use your identifiable specimens or data for future research, our study will be reviewed and approved by an Institutional Review Board who will make sure that we are

protecting your confidentiality. These future studies might help us better understand SCLS or other diseases or conditions. This could include studies to develop other research tests, treatments, drugs, or devices, that may lead to the development of a commercial product by the NIH and/or its research or commercial partners. There are no plans to provide financial compensation to you if this happens. Also, it is unlikely that we will learn anything from these studies that may directly benefit you.

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

We may share your specimens and data with other researchers. The other researchers may be doing studies in similar areas to this study or in other unrelated areas. These researchers may be at NIH, other research centers and institutions, or at commercial entities.

One way that we may share your data is by putting it into a large database called a repository, which is a way to make it widely available to the research community. If we do place your data in a repository, it will be labeled with a code (not with your name or other information that could be used to easily identify you). Even though it will only be labeled with a code, some types of data, in particular data about your genes (called genetic or genomic data), can be used to figure out who you are, although this is difficult to do, and we think it is unlikely to happen.

The data in the repository will be widely available to anyone who wants it.

If we do share your specimens or data, we will know that the specimens and data came from you. However, the other researchers will not know that they came from you (i.e., they will be de-identified).

In addition to the planned use and sharing described above, we might remove any labels from your specimens and data that might identify you (i.e., anonymize them), and use them or share them with other researchers for future studies at the NIH or other places. When we or the other researchers use your anonymized specimens and data for these projects, there will be no way to know that they came from you. We want to make sure that you understand that this is a possibility if you participate in this study. Once we do this, we would not be able to remove your specimens or data from these studies or prevent their use in future studies because we would not be able to tell which specimens or data belong to you.

Risks of storage and sharing of specimens and data

When we store your specimens and data, we take precautions to protect your information from others who should not have access to it. When we share your specimens and data, we will do everything we can to protect your identity, for example, when appropriate, we remove information that can identify you. Even with the safeguards we put in place, we cannot guarantee that your identity will never become known, or that no one will gain unauthorized access to your information. New methods may be created in the future that could make it possible to re-identify your specimens and data.

Can you change your mind about use and sharing for future research?

If you change your mind and do not want us to store and use your specimens and data for future studies, you should contact the study team. We will do our best to comply with your request but cannot guarantee that we will always be able to destroy your specimens and data. For example, if some research with your specimens and data is already complete, the information from that

research may still be used. Also, if the specimens and data have been shared already, it might not be possible to withdraw them.

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

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

PAYMENT

Will you receive any type of payment for taking part in this study?

You will be compensated for participating in this study as follows:

- $50 for the initial evaluations
- $20 for any follow-up evaluations or telehealth evaluations
- $30/day for clinical digital photography
- $50 for the blood draws
- $50 for skin prick/intradermal testing
- $150 for leukapheresis
- $100 for each skin biopsy
- $100 for cardiac MRI

You will be paid by check, debit card, direct deposit, or automated clearing house (ACH). If you are unable to finish the study, you will receive compensation as described above for the parts you completed.

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

REIMBURSEMENT

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

NIAID will cover some or all of your travel expenses related to participation in this study. This may include direct payments or reimbursements for expenses related to transportation, lodging, and meals. The amount and form of these payments are determined by the NIAID Central Travel Policy for Research Protocol Participants. We will give you a copy of this policy.

If your travel to the NIH Clinical Center (e.g., flight, hotel) is arranged and paid for by the NIH, the agency making the reservations and their representatives will have access to your identifiable information.

To receive payment and/or reimbursement, you may be asked to provide your Social Security number. If you do not provide one, you can still participate in the study, but you may not be able to receive payment and/or reimbursement.

COSTS

Will taking part in this research study cost you anything?

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

CONFLICT OF INTEREST (COI)

The NIH reviews NIH staff researchers at least yearly for conflicts of interest. This process is detailed in a COI Guide. You may ask your research team for a copy of the COI Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines or the guidelines of their home institution, but they do not need to report their personal finances to the NIH.

The NIH and the research team for this study are using a drug developed by PharmAbcine, Inc. through a collaboration between your study team and the company. This drug is only being used for laboratory tests and is not being given to any humans on this study. The company also provides financial support for this study.

CLINICAL TRIAL REGISTRATION AND RESULTS REPORTING

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

CONFIDENTIALITY PROTECTIONS PROVIDED IN THIS STUDY

Will your medical information be kept private?

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

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

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

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

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

Certificate of Confidentiality

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

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

The Certificate does not protect your information when it:

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

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

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

Privacy Act

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

POLICY REGARDING RESEARCH-RELATED INJURIES

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

PROBLEMS OR QUESTIONS

If you have any problems or questions about this study, about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Dr. Kirk Druey, at 301-435-8875 or kdruey@niaid.nih.gov. You may also contact the study coordinator: Robin Eisch, at 301-443-1720 or robin.eisch@nih.gov. You may also call the NIH Clinical Center Patient Representative at 301-496-2626, or the NIH Office of IRB Operations at 301-402-3713, if you have a research-related complaint or concern.

CONSENT DOCUMENT

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

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

Signature of Research Participant	Print Name of Research Participant	Date

Investigator:

Signature of Investigator	Print Name of Investigator	Date

Witness should sign below if either:

1. **A short form consent process has been used to enroll a non-English speaking subject or**
2. **An oral presentation of the full consent has been used to enroll a blind or illiterate subject**

Signature of Witness	Print Name of Witness	Date

NIH ADMINISTRATIVE SECTION TO BE COMPLETED REGARDING THE USE OF AN INTERPRETER:

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent and served as a witness. The investigator obtaining consent may not also serve as the witness.

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent but did not serve as a witness. The name or ID code of the person providing interpretive support is: _____.

PRINCIPAL INVESTIGATOR: Kirk M Druey, MD

STUDY TITLE: Studies in the Pathogenesis of Systemic Capillary Leak Syndrome

STUDY SITE: NIH Clinical Center

Cohort: Assent

Assent Version: 2 May 2023

You or your relative has a disease called systemic capillary leak syndrome (SCLS), which means you or your relative may have an episode of a drop in blood pressure and swelling of arms and legs due to leakage of fluids and proteins into the tissues. We want to learn more about SCLS by examining your blood fluids and blood cells.

You will be asked to allow the doctors at NIH to see you. If you are unable to come to NIH, we may talk to you on the phone, and may ask your doctor at home for blood. At the doctor's visit, we will ask you to take some tests. We will take blood from your arm. A large rubber band will be tied on your arm. We can use medicine on your skin so the blood draw does not hurt much. A needle will be put through your skin to draw blood from your vein. Approximately twenty teaspoons will be removed. Sometimes blood drawing causes a bruise. Less commonly, blood drawing causes an infection.

In addition to routine blood tests, we may ask you permission to draw research blood samples to see if you have changes in the genetic material that may influence the growth and function of your blood cells and capillary cells. If you agree to give a blood sample for this genetic test, the amount taken will be about six teaspoons. This test is usually done once. All information about the study or genetic testing is kept in locked study files and will remain private. If you have any questions, please talk to the study doctor or nurse.

DNA lives in every cell and is like your body's cookbook. The recipes for growth and development are called "genes." We all have thousands of genes. Your DNA may or may not tell us what is causing health problems. If another NIH study has your DNA, we may use information from your DNA to look for changes that can cause health problems. Even if these tests do not help you or your family, they could help other people. If we learn genetic information important for your health, then we will tell you and your parents.

If you have SCLS and are at least 8 years old, we may also ask for a bone marrow (liquid inner portion of bone) sample to learn about your disease and see if you have changes to the genetic material that may influence blood and capillary cell growth and function. The purpose of this procedure is to collect cells from your bone marrow. First, you will be offered medicine to help you relax and possibly feel sleepy. Another medicine will be given through your vein to decrease pain. We will then place a needle in your hipbone. We will also remove a small piece of bone from the same area. Your skin will be numbed with medicine before this is done. The numbing medicine is put in with a very small needle, and may sting. This medicine will make the pain less, but it still might hurt a little. The pain may be sharp as from a needle, aching as from a

toothache, and last at most several hours after the bone marrow sample. We will use the bone marrow sample as part of your medical care and to understand SCLS better.

If you are at least 16 years old, you may have pricks to your skin or injections under your skin with a small needle to see if you have allergies. This is called a Skin Test. If you are allergic, you might feel itching or swelling, like a mosquito bite, where the needle touched your skin. The itching or swelling will not last very long and should go away in about 30-60 minutes.

If you have SCLS and need a biopsy of another part of your body to identify or treat a problem, we may ask for extra tissue for research purposes during that procedure. After the identification and treatment tests are completed, any leftover tissue from the biopsy procedure may be used for research purposes.

If you have SCLS and are 16 years of old, you may have a skin biopsy. A skin biopsy procedure might hurt. You might bleed a little, and you may have a scar after your skin heals. Less commonly, the place where the biopsy is done may become infected. If this occurs, you may receive medicine to help you heal from infection.

If you are at NIH, we may want to take pictures, and measure the temperature of your skin. This does not hurt, but the stickers we use to measure your temperature may make your skin red or itchy. If this happens, we will remove them.

You may not need to come to the National Institutes of Health for an appointment. It is possible for the NIH study doctors to see you and your family using your family's computer. We can talk to you and your family about your health over the computer. Your family, your doctor, or other healthcare provider can send the blood or biopsy samples collected from you to our hospital for research testing if you cannot come to the NIH.

During your participation in this study, any blood, skin, and bone marrow biopsy samples that are collected may be stored for future research. These samples may help us learn more about SCLS or related conditions. The research tests we will use may not be like medical tests. If you have any questions, please talk to your doctor or nurse.

If you do not want to be a part of this study, that is okay, and you and your parents can tell us if you later want to participate.

During the time you take part in this study, we will inform you of any new information regarding your condition.

I have had this study explained to me in a way that I understand, I have been given the opportunity to discuss it, and I have had the chance to ask questions. I agree to take part in this study.

Assent of Participant:

_____	_____	_____
Signature of Participant	Print Name of Participant	Date

Investigator:

_____	_____	_____
Signature of Investigator	Print Name of Investigator	Date