INFORMED CONSENT FORM AND HIPAA AUTHORIZATION

TITLE: A Comparison of Individualized vs. Weight Based Protocols to Treat Vaso-Occlusive Episodes in Sickle Cell Disease

PROTOCOL NO.: IRB Protocol # 20191554

NCT NO.: NCT03933397

SPONSOR: National Heart, Lung, and Blood Institute National Institutes of Health

CONCISE SUMMARY

The purpose of this research study is to compare two different protocols for opioid pain medicine to treat sickle cell disease pain that is severe enough to send patients to the emergency department for treatment. One way uses your weight to decide how much pain medicine to give you while in the emergency department. This is called weight based treatment. The other way uses how much pain medicine you take at home and how much medicine you needed during past emergency department visits to decide how much medicine to give you. This is called patient specific treatment.

You will be in the study until you have an emergency department visit for your sickle cell disease pain that uses the weight based treatment or patient specific treatment or until the study ends in two years. During your emergency department visit, the doctor can tell you what pain medication you are getting (morphine or hydromorphone) but cannot tell you if you are on the weight based treatment or the patient specific treatment.

Your participation will end when you are discharged to home, or if you are admitted to the hospital, transferred to the observation unit or until you have been in the emergency department for 6 hours – whichever comes first. You will be asked questions about how you are feeling and about your pain. The research assistant will write down your blood pressure, heart rate, breathing rate and oxygen levels.

Seven days after your emergency department visit, the research assistant will look at your medical record to see if you were admitted to the hospital, had any emergency department visits or day hospital visits. There are risks to the drugs used in this study. The risks are described in this document. Some risks include nausea/vomiting, itching, drowsiness, light headedness, low blood pressure and slowed breathing.

If you are interested in learning more about the study, please continue to read the information in this form.

CONSENT TO PARTICIPATE IN A RESEARCH STUDY

You are being asked to take part in this research study because you have sickle cell disease (SCD) and may have to go to the Emergency Department (ED) in the future for sickle cell disease pain. Research studies are voluntary. This means you are free to decide if you want to be in the study. This document may contain words and information that you do not understand. Please ask your study doctor or study staff to explain anything that is not clear to you. We encourage you to talk with your family and friends before you decide to be in the study. Side effects (bad reactions to the drugs you are given) may occur. Other important information about the research study is listed below.

Please tell the study doctor or study staff if you are taking part in another research study.

This study is paid for by a grant from the National Institutes of Health (NIH). Portions of the study doctor and Dr. Paula Tanabe's (PhD) at Duke University, Dr. Huiman Barnhart's (PhD) at Duke University and their research teams at Duke University's salaries will be paid by this grant. <<CF-Main Financial Disclosure>>

WHY IS THIS STUDY BEING DONE?
Management of bad pain from sickle cell disease is the most common reason for sickle cell patients to visit the emergency department. There are many ways to treat bad pain from sickle cell disease in an emergency department that are not based on research. Many times, patients who come to the emergency department with sickle cell pain feel that they do not have enough pain control. The purpose of this study is to compare two ways to treat bad pain in the emergency department for adults with sickle cell disease. Neither clinically relevant research results nor individual research results will be disclosed to you. This study is considered investigational.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?
The study is for about 460 adult sickle cell disease patients with an emergency department visit for bad pain. The study will be done at six different hospitals in the United States. After 230 adults have an emergency department visit for bad pain, the study will end. Those who are a part of the study but did not have an emergency department visit will be told by phone, a later clinic visit or by mail that the study is over.

WHAT IS INVOLVED IN THE STUDY?
Study Enrollment
If you decide to be in this study, you will be asked to sign, date and time this consent form. You will also be asked for your date of birth, age, race, gender, ethnicity, sickle cell type (genotype). You will also be asked your doctors names, about your medicines, and how many times you went to the emergency department and hospital in the last year. You will be asked how long you went to school, if you are working and how much money you are making. You will be randomly assigned (like a coin toss) to receive care for your bad pain at your next emergency department visit using the patient-specific pain treatment or weight-based pain treatment. You have an equal chance of being in either group. Your hematologist/sickle cell care team will know which group you are in. At your next emergency department visit for bad sickle cell disease pain, you will be told what drug and what dose are ordered for you. You will not be told if you are in the patient-specific treatment or weight-based treatment. You may or may not benefit by participating in this study.

Emergency department care
In the emergency department, you will be asked about your pain every 30 minutes. Additional medicines may be given as needed every 20-30 minutes. Medicines will include opioids (strong pain medicines that may be called narcotics), either morphine or

hydromorphone (also called Dilaudid). The medicines will be given intravenously (IV) or under the skin. These pain medicines may be given to you in higher doses than you would normally take, or more often.

Pain management protocols

Patient-specific protocol group

If you are assigned to this group, members of your healthcare team will write a pain treatment plan just for you. The plan will be based on the pain medicines you take at home, and what was needed during your past hospital and emergency department visits to treat your pain. This plan will be used the next time you come to the emergency department for bad sickle cell disease pain. The plan will include the specific medicines, doses of those medicines, how often you should receive them and how you will receive them. The plan will be written by your hematologist/sickle cell team and will be available to Emergency Medicine doctors.

Weight-based protocol group

If you are randomized to this group, members of your healthcare team will write a pain treatment plan just for you based on your weight. This plan will be used the next time you come to the emergency department for bad sickle cell disease pain. The plan will include the specific medicines and their doses. The plan will be written by your hematologist/sickle cell team and will be available to Emergency Medicine doctors. The first dose of pain medicine will be based on your weight.

ED Visit Interviews: At the first emergency department visit for bad sickle cell disease pain, you will be asked questions about your pain and symptoms. This will take about 5 minutes. You will be asked again about every 30 minutes until you are admitted to the hospital, discharged home, transferred to observation status or for a maximum of 6 hours, whichever comes first. Research staff will also take your blood pressure (using a blood pressure cuff), check your oxygen saturation (by placing a probe on the outside of your finger) and measure your level of fatigue.

When you leave the emergency department (whether you are discharged to home, transferred to a different hospital, or admitted to the hospital), you will be asked a few questions about how you feel about the pain treatment you received.

Medical record review: 7 days after you leave the emergency department, research staff will review your chart and write down all medicines you received, and any follow-up emergency department visits or hospitalizations you may have had.

Summary of the differences of being in this study compared to your usual care

By participating in this research study, your pain management may be better than usual care because both treatment plans suggest giving medicines more often and at higher doses than what you may receive in many emergency departments.

HOW LONG WILL I BE IN THIS STUDY?
Your participation will end after your next emergency department visit for bad sickle cell disease pain, up to 2 years, or until the study ends, whichever comes first. Participation in the study does not require you to come to the emergency department, it only decides how your pain will be managed if you come to the emergency department for treatment of bad sickle disease pain.

You can choose to stop participating at any time without penalty or loss of any benefits to which you are otherwise entitled. However, if you decide to stop participating, we encourage you to talk to your doctor first.

If you choose to stop participating, or after the study has been completed, the emergency department physician will treat your sickle cell pain as they usually do (usual care).

WHAT ARE THE RISKS OF THE STUDY?
As a result of your participation in this study, you are at risk for the following side effects. You should discuss these with the study doctor and your regular health care provider if you choose.

Morphine Sulfate or Hydromorphone may cause some, all or none of the side-effects listed below.

<u>More likely</u>

- Drowsiness and sedation, preventing you from being alert or staying awake
- Nausea, vomiting
- Itching
- Light-headedness
- sedation
- sweating/flushing
- euphoria
- dry mouth

<u>Less Likely</u>

- Respiratory depression (breathing is slowed or stops in severe cases)
- Low blood pressure
- apnea
- circulatory depression
- cardiac arrest
- and shock

There is also the risk that participating in this research study may provide less pain control than you normally experience. It is also possible that you may experience more side effects if you receive higher doses than you would normally receive using the pain treatment plans in this study. However, you will be carefully monitored to reduce these risks. To minimize side effects, the nurse and doctor in the emergency department will check your pain levels and any reaction to the pain medicines. In addition, the research assistant will check your blood pressure, pain and sleepiness levels, breathing and oxygen level about every 30 minutes.

There is also a potential risk of loss of confidentiality. Every effort will be made to keep your information confidential; however, this cannot be guaranteed. You may refuse to answer any of the questions and you may take a break at any time during the study. You may choose to stop being a part of this study at any time.

There may be risks, discomforts, drug interactions or side effects that are not yet known.

WHAT IF I AM PREGNANT?
Opioids are not associated with birth defects, but may cause the baby to move less and slow down his/her heart rate, however there may be unexpected risk. Opioids are often used to treat pregnant women with severe pain, including women with sickle cell disease. Treating your pain with opiates is recommended by the American College of Obstetricians and Gynecologists. You can participate in this study if you are pregnant.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?
If you agree to take part in this study, it is possible that your pain may be managed better than if you were not part of this study. Both the patient-specific and weight-based treatment plans may offer you better, or faster pain control than what you normally experience during an emergency department visit. If you are assigned to the patient-specific treatment plan, you may receive better or faster pain relief compared to the weight-based treatment plan. The information learned from this study will benefit other individuals living with sickle cell pain who come to the emergency department for pain management.

ARE THERE ALTERNATIVES TO TAKING PART IN THE STUDY?
If you decide that you do not want to take part in this study, you will be treated according to usual care practices for patients with sickle cell disease pain. These treatments may include opioids, such as morphine or hydromorphone (also known as Dilaudid), and other pain medicines such as ketorolac or ibuprofen. Please talk to your doctor about these and perhaps other options, and their risks and benefits.

WILL MY INFORMATION BE KEPT CONFIDENTIAL?

Study records that identify you will be kept confidential as required by law. Federal Privacy Regulations provide safeguards for privacy, security, and authorized access. Except when required by law, you will not be identified by name, social security number, address, telephone number, or any other direct personal identifier in study records disclosed outside of the study site. The research team from Duke and the Duke Clinical Research Institute (DCRI) will have access to your study files and informed consent; they are required to review these documents to make sure your research site is complying with ethical practices. Your consents will stay at the study site. However, a copy of your signed consent form may be temporarily uploaded to a password-protected, secure, encrypted cloud based system (Duke-Box) to allow the DCRI monitor(s) to review the signed form. As soon as the consent form is reviewed by the monitor, the form will be permanently deleted from the system. You will be assigned a unique code number. The key to the code will be kept on a secure computer network drive behind a password-protected firewall at the study site. Only study personnel at each respective study site, including the research assistants who will be conducting the interviews will have access to your personal identifier information. Duke will receive de-identified information only via a web-based data system. No identifiable information will be included in the database. You have the right to access your own Personal Health Information (PHI) at any time.

A Certificate of Confidentiality from the National Institutes of Health covers this research. The COMPARE_VOE researchers at Duke University may not share or use information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or used as evidence without your consent to do so. Information that might identify you cannot be shared with anyone who is not connected with the research unless there is a federal, state or local law that required sharing your information. An example that would require information that might identify you to be shared would be to report child abuse or communicable diseases. Information that could identify you can be shared if you have consented to share identifying information, including your medical treatment, or if your information is used for other scientific research, as allowed by federal regulations protecting research subjects.

As part of the study, Dr. Tanabe, Dr. Barnhart, and their study team will report the results to the National Institutes of Health. In addition, your records may be reviewed in order to meet federal or state regulations. Reviewers may include representatives of the National Institutes of Health, <<CF-Main SMO Company 1>><<CF-Main Affiliated IN Language 1>>the United States Food and Drug Administration (FDA), the Institutional Review Board (IRB) that reviewed this research, or the Duke University Health System Institutional Review Board. If any of these groups review your research record, they may also need to review your entire medical record.

These people may look at your records to make sure the study has been done the right way. They also want to make sure that your health information has been collected the right way, or for other reasons that are allowed under the law.

The study results will be retained in your research record for at least six years after the study is completed. At that time the research information not already in your medical record will be destroyed or information identifying you will be removed from such study results at Duke Clinical Research Institute. Any research information in your medical record will be kept indefinitely.

This information may be further disclosed by the sponsor of this study, National Institutes Health, or by outside reviewers for audit purposes. If disclosed by the sponsor or outside reviewers, the information is no longer covered by the federal privacy regulations.

While the information and data resulting from this study may be presented at scientific meetings or published in a scientific journal, your identity will not be revealed.

WHAT ARE THE COSTS?
There will be no additional costs to you as a result of being in this study beyond what you normally pay for an emergency department visit. You may talk to the study staff and your insurance company about what is covered.

WHAT ABOUT COMPENSATION?
If you have an emergency department visit for bad sickle cell disease pain during the study period, you will be compensated $XX.00.

OR You will not receive any payment for taking part in this research study.

<<CF-Main Payment for Part. Paragraph>>

WHAT ABOUT RESEARCH RELATED INJURIES?
If you are injured or get sick because of being in this research, call the study doctor immediately. The study doctor will provide medical treatment or refer you for treatment. Immediate necessary medical care will not be available at Duke University Medical Center in the event that you are injured as a result of your participation in this research study. There is no commitment by Duke University, Duke University Health System, Inc., to provide monetary compensation or free medical care to you in the event of a study-related injury.

Immediate necessary medical care is available at the study site in the event that you are injured as a result of your participation in this research study. However, there is no

commitment of the study site physicians to provide monetary compensation or free medical care to you in the event of a study-related injury.

For questions about the study or research-related injury, contact the study doctor. If you have other questions about the study, you can also contact Dr. Paula Tanabe (Duke University) at (919) 613-6038 during regular business hours and at (312) 502-0185 after hours and on weekends and holidays.

WHAT ABOUT MY RIGHTS TO DECLINE PARTICIPATION OR WITHDRAW FROM THE STUDY?

You may choose not to be in the study, or, if you agree to be in the study, you may withdraw from the study at any time. If you choose to withdraw during an emergency department visit, notify the doctor taking care of you. If you do decide to withdraw permanently (all future visits), we ask that you notify the study doctor.

If you withdraw from the study, no new data about you will be collected for study purposes other than data needed to keep track of your withdrawal or if you have a side effect related to the study. All data that has already been collected for study purposes will be sent to the study sponsor (National Institutes of Health).

Your decision not to participate or to withdraw from the study will not involve any penalty or loss of benefits to which you are otherwise entitled and will not affect your access to health care at the study site.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

Your doctor or the sponsor may decide to take you off this study if your condition gets worse, if you have serious side effects, or if your study doctor determines that it is no longer in your best interest to continue. The sponsor or regulatory agencies (such as, the FDA) may stop this study at any time without your consent. Reasons why this might occur include stopping the study for safety reasons, the funding for the study runs out or the study has enrolled and treated enough patients to answer the research question.

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.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or a research-related injury, or if you have problems, concerns, complaints, questions or suggestions about the research, contact the research team at the phone number(s) listed above on the first page. Dr. Tanabe may

also be contacted at (919) 613-6038 during regular business hours and at (312) 502-0185 after hours and on weekends and holidays.

This research is being overseen by an Institutional Review Board ("IRB"). An IRB is a group of people who perform independent review of research studies. The goal of the IRB is to protect the rights and welfare of study subjects. You may talk to them at (888)-303-2224 or (800) 562-4789, irb@cgirb.com if:

- You have questions, concerns, or complaints that are not being answered by the research team.
- You are not getting answers from the research team.
- You cannot reach the research team.
- You want to talk to someone else about the research.
- You have questions about your rights as a research subject.

STATEMENT OF CONSENT

"The purpose of this study, procedures to be followed, and the study's risks and benefits have been explained to me. I have been allowed to ask questions, and my questions have been answered to my satisfaction. I have been told whom to contact if I have questions, to discuss problems, concerns, or suggestions related to the research, or to obtain information or offer input about the research. I have read this consent form and voluntarily agree to be in this study, with the understanding that I may withdraw at any time. I have been told that I will be given a signed and dated copy of this consent form<<CF-Main California Bill of Rights>>."

_____ _____ _____
Signature of Subject Date Time

_____
Printed Name of Subject

_____ _____ _____
Signature of Person Obtaining Consent Date Time

_____
Printed Name of Person Obtaining Consent

HIPAA AUTHORIZATION

Federal regulations give you certain rights related to your health information. These include the right to know who will receive the information and how it will be used. The study doctor must obtain your authorization (permission) to use or release any health information that might identify you.

WHAT INFORMATION MAY BE USED AND SHARED?

The study doctor and study staff will use and share your health information as part of this research study. Except when required by law, you will not be identified by name, address, telephone number or other facts that could identify the health information as yours.

Examples of the information that may be used are:

- Medical records (from any doctor, hospital or other healthcare provider)
- Information created or collected during the research. This could include your medical history, and dates or results from any physical exams, laboratory tests or other tests.

WHO WILL RECEIVE INFORMATION ABOUT YOU?

The study doctor and study staff will share your personal health information with:

- the sponsor, including persons or companies working for or with the sponsor
- Independent/Institutional Review Board (IRB) <<CF-Main SMO Company 2>><<CF-Main Affiliated IN Language 2>>
- the U.S. Food and Drug Administration (FDA)
- Department of Health and Human Services (DHHS) agencies
- other regulatory agencies

WHY WILL THIS INFORMATION BE USED AND/OR GIVEN TO OTHERS?

The sponsor and the groups above will use your health information:

- to complete this research
- to evaluate the results of the study
- to check that the study is being done properly
- to obtain marketing approval for new products resulting from this research

IS MY HEALTH INFORMATION PROTECTED AFTER IT HAS BEEN GIVEN TO OTHERS?

Your health information may be further shared by the groups above. If shared by them, the information will no longer be covered by this Authorization. These groups are committed to keeping your health information confidential.

WHAT IF I DECIDE NOT TO ALLOW THE USE OF MY HEALTH INFORMATION?

You do not have to sign this form. If you do not sign this form, you cannot take part in this research study.

MAY I WITHDRAW OR REVOKE (CANCEL) MY PERMISSION?

YES. You may withdraw your permission to use and disclose your health information at any time. You can do this by sending written notice to the study doctor. If you withdraw your permission, you will not be able to continue being in the research study.

WHAT HAPPENS IF I WANT TO WITHDRAW MY AUTHORIZATION?

Information that has already been gathered may still be used and given to others. If you withdraw your permission, no new health information will be gathered unless you have a side effect related to the study.

If you withdraw from the study but do not withdraw your Authorization, new health information may be collected until this study ends.

WILL MY AUTHORIZATION EXPIRE?

If you do not withdraw this Authorization, it will remain in effect.

If the research site is located in California, Delaware, Indiana, Washington, or Wisconsin this authorization will expire on 31Dec2060.

There is no expiration of this authorization except for research conducted in the states listed above.

MAY I REVIEW OR COPY THE INFORMATION OBTAINED OR CREATED ABOUT ME?

YES. You have the right to review and copy your health information. However, your access to this information may be delayed until the study is complete.

Your decision to withdraw your Authorization or not to participate will not involve any penalty or loss of access to treatment or other benefits to which you are otherwise entitled.

AUTHORIZATION

By signing this form, I allow the use or disclosure of my health information. I will receive a signed and dated copy of this Authorization.

Printed Name of Subject

Signature of Subject **Date**