

RESEARCH SUBJECT INFORMATION AND CONSENT FORM

TITLE: Joint Health Study

PROTOCOL NO.: None
WIRB® Protocol #20172413

SPONSOR: Bloodworks Northwest

INVESTIGATOR: Rebecca Kruse-Jarres, MD, MPH
921 Terry Avenue
Seattle, WA 98104
United States

STUDY-RELATED PHONE NUMBER(S): Rebecca Kruse-Jarres, MD, MPH
206-689-6507
206-292-6525, option 3

Heidi Thielmann, PhD
206-689-6234

SUB-INVESTIGATORS: Bruno Steiner, PT
Barbara A. Konkle, MD
Jill Johnsen, MD
Jezzamine Choi, MN, ARNP

STUDY COORDINATORS: Sarah Galdzicka
Shannon Lynch
Maggie Moore, RN
Sarah Ruuska, MPH
Sophie Schmitter
Heidi Thielmann, PhD

SUMMARY

We are asking you to be in a research study. The purpose of this consent form is to give you the information you will need to help you decide whether to be in the study or not. You should not join this research study until all of your questions are answered.

Things to know before deciding to take part in a research study:

- The main goal of a research study is to learn things to help patients in the future.
- The main goal of standard medical care is to help identify and treat patients' medical conditions.

- The decision to join or not join the research study will not cause you to lose any medical benefits. If you decide not to take part in this study, your doctor will continue to treat you as he/she usually would.
- Parts of this study may involve standard medical care. Standard medical care is the treatment normally given for a certain condition or illness.
- After reading the consent form and having a discussion with the research staff, you should know which parts of the study are experimental and which are standard medical care.
- Your medical records may become part of the research record. If that happens, your medical records may be looked at or copied by the sponsor of the study. They may also be looked at or copied by other groups associated with the study.
- Your medical insurance may be billed for any standard medical care you receive during the research study. Insurance companies may not pay for treatment that is part of a research study. Taking part in a research study could affect your current or future insurance coverage.

If you take part in this research study, you will be given a copy of this signed and dated consent form.

PURPOSE OF THE STUDY

Hemophilia B can be associated with damage to the joints because of bleeding. This study may help us see earlier signs of joint damage or bleeding by using ultrasound and may help us assess whether these changes correlate with biomarkers in the blood. The current standard of care for detecting acute bleeding in joints is a physical exam done by your doctor or physical therapist and sometimes x-rays and MRIs; however, a physical exam and x-rays may not be able to detect joint damage caused early on and MRIs are costly, not easily accessible, and take a significant time commitment. Ultrasound can identify acute bleeding in the joint or soft tissue and it can differentiate bleeding from other musculoskeletal problems. Ultrasound can also show early joint damage due to bleeding and we can follow that damage over time.

During this study we would like to examine whether or not having a higher trough during your prophylactic treatment with clotting factor offers better joint protection than the standard trough of 1% Factor IX (FIX or Factor 9). We would also like to learn more about diagnosing joint damage earlier by using ultrasound to better understand the relationship between musculoskeletal ultrasound measurements, your medical history, activity level, joint assessment, quality of life, and biomarkers in your blood. We hope to learn how to identify differences between acute bleeding in the joints from other non-bleeding related problems in the joints.

This is a prospective, non-randomized controlled study. You will be included in one of three groups depending on your current treatment with the intent to stay on this treatment regime for the next three years. The three groups are as follows:

- Group A: episodic treatment with FIX concentrates for bleeding episodes
- Group B: prophylaxis using any FIX concentrated with an intended trough of 1-5%
- Group C: prophylaxis with an extended half-life FIX with an intended trough of > 10%

PROCEDURES

We are asking you to participate in this study because you have Hemophilia B and are receiving one of the treatment regimens listed above. If you agree to participate in this study, your care provider or a research coordinator will interview you about your medical history, activity and functional level, pain, and quality of life. You can choose not to answer any question that you do not want to answer. We anticipate that completing the interview and questionnaires will take about 1 hour. The ultrasound will take 1-2 hours, and this will be done as a research procedure. Other research procedures include assessments and blood draws during your initial (baseline) visit and at 1-, 2-, and 3-years after your initial visit. Because x-rays and MRIs are standard of care, we want to compare the information obtained from x-rays and MRIs with information from the ultrasound imaging; therefore, the first ten subjects will have x-rays and MRIs. The x-rays will take about 45 minutes and the MRI will take up to 2 hours. Both the x-rays and MRI are research procedures and will be paid for by the study.

We will also review your medical record to gather information such as your bleeding disorder diagnosis, severity of your disorder, treatments, bleeding history, and other past medical and surgical history.

If you have an acute pain event during the course of this research study, we encourage you to come in during and after the acute pain event to complete some assessments. Visits for the first acute pain event and the first post-acute pain event are considered research procedures and will be paid for by the study. Visits for the second or more acute pain events and second or more post-acute pain events are standard medical care and will not be paid for by the study.

Details about the research procedures are described below along with an assessment schedule for the research procedures.

Questionnaires, Assessments, and Blood Draws

We ask you to complete the following questionnaires, assessments, and blood draws at your first visit and at each annual exam:

- Baseline Form (demographics, bleeding history, use of hemostatic agents, past medical/surgical history, vital signs)
- Rapid Assessment of Physical Function (RAPA): 1 page questionnaire to assess physical activity
- Hemophilia Activity List (HAL): 3 page self-administered questionnaire
- Veritas – Pro (Arms B and C only)
- Brief Pain Inventory (BPI): 10 question self-administered
- Joint Assessment (Hemophilia Joint Health Score = HJHS)
- Ultrasound (MSKUS): prior exams up to 3 months are permissible
- X-rays and MRIs (first 10 subjects only): prior exams up to 6 months are permissible
- Blood draws for labs: Factor XI level, Factor XI inhibitor, hsCPR
- Blood draws for plasma sample for biomarkers for biomarker repository

Historical assessments up to one year will be allowed as long as all required data was collected.

Ultrasound Assessment: Ultrasound techniques are safe procedures that use low-power sound waves to view inside the body. Because ultrasound images are captured in real-time, they can also show movement of the body's internal organs as well as blood flowing through blood vessels. Unlike x-ray imaging, there is no radiation used in ultrasound imaging. In an ultrasound exam, a transducer or probe is placed directly on the skin. A layer of gel is applied to the skin so that the ultrasound waves can be transmitted from the probe through the gel into the body. The gel may feel cool to the touch. The ultrasound image is created based on the reflection of the waves off of the body structures such as blood flowing through vessels, tendons, muscles, nerves, ligaments, soft tissue, and bone. In addition to the research-related ultrasounds, we may be interested in reviewing ultrasounds and related data you completed for your clinical care up to three months prior to your entrance into this study.

X-ray Assessment: The first ten subjects will have x-rays of their target joint and the joint on the opposite side at baseline and 1 year later. X-ray images taken within six months of study visits are permissible. An x-ray uses radiation to take pictures of bones. You may be asked to remove your clothes and wear a gown if your clothes cover the areas we want to x-ray. You will need to stand, sit, or lay very still in order to not blur the x-ray. You may be asked to hold your breath for a few seconds while the x-rays are being taken. We will use the following views:

- Knee – radiographs: standard AP and lateral, but also include a merchant view (3 views total)
- Elbow – radiographs: standard AP and lateral (2 views)
- Ankle – radiographs: standard AP, lateral, and mortise (3 views)

MRI Assessment: The first ten subjects will have magnetic resonance imaging (MRI) images of their target joint and the joint on the opposite side at baseline and 1 year later. MRI images taken within six months of study visits are permissible. The MRI device utilizes a magnetic field and radio waves to create images. The MRI images will be made while you lie on a narrow bed placed inside of a large magnet.

Blood work: We will draw up to 40 mL (3 tablespoons) of blood to test your factor level, inhibitor level, and biomarkers.

Assessment of painful episodes: We encourage you to come in for an assessment during a painful episode of either of your elbows, knees or ankles. This assessment may take 1-2 hours. We will ask you to classify the episode as a bleed vs. non-bleed. A healthcare practitioner will examine the pertinent joint and classify it as a bleed vs. non-bleed and treatment will be determined according to the exam. You will then undergo an ultrasound and your treatment plan will be reviewed. If changes are made based on the ultrasound findings, we will note these changes. We encourage you to come in during each painful episode and we will include the data in our analysis; however, we will compensate you for only the visit for your first painful episode as only the visit for the first painful episode is considered for research. Visits for subsequent pain events are considered standard of care.

Assessment post-painful episodes: If you have had a painful episode, we encourage you to return to clinic within 1-2 weeks for a repeat exam and ultrasound which may take 1-2 hours. We encourage you to come in after each painful episode and we will include the data in our analysis;

however, we will compensate you for only the visit for your first post-painful episode as only the visit for the first post-painful episode is considered for research. Visits for subsequent post-painful events are considered standard of care.

Biomarker Repository: During all visits, including acute pain and acute pain follow-up visits, we will ask if you would like to contribute blood samples for the repository. If you agree, we will collect an additional five tubes of blood (15 mL). You do not have to contribute samples to this biomarker repository if you do not want to.

Assessment Schedule:

	Baseline	Acute Pain Event	Post-Pain Event	Years 1 and 2	Year 3
Demographics (age, race/ethnicity)	X			X	X
History (including bleeding history, medications, hemostatic agents and regimen, surgeries, joint bleeding/injury/surgery)	X	X	X	X	X
Recent joint bleeding/injury history (over the last 1 year)	X			X	X
Activity level (e.g. RAPA or fitbit)	X	Optional	Optional	X	X
Functional assessment (HAL)	X	Optional	Optional	X	X
Brief Pain Inventory (BPI)	X	X	X	X	X
Physical Exam	X	X	X	X	X
Hemophilia Joint Health Score (HJHS)	X	Optional	Optional	X	X
Ultrasound (MSKUS)	X	X	X	X	X
Blood work (biomarkers)	X	X	X	X	X
X-ray (1 st 10 patients only)	X			X*	
MRI (1 st 10 patients only)	X			X*	
Veritas or Veritas-Pro - Adherence	X	Optional	Optional	X	X

* Year 1 only

RISKS AND DISCOMFORTS

Physical Risks

Ultrasound

There are no known risks to ultrasound. The gel may be sticky but the test should not cause any pain or discomfort. Ultrasound does not use radiation.

X-ray

The cumulative radiation exposure from x-rays is considered small and is not likely to adversely affect you or your bleeding disorder. However, the effects of radiation add up over a lifetime. It

is possible that having several of these tests may add to your risk of injury or disease. When deciding to enter this study, think about your past and future contact with radiation including x-rays taken for any reason.

MRI

Some people cannot have MRIs because they have some type of metal in their body. For example, if you have metal implants, a heart pacemaker, or artificial heart valves you cannot have an MRI. During the MRI, you will lie in a small closed area inside a large magnetic tube. Some people are scared or anxious in small places (claustrophobic). The MRI scanner makes loud banging noises while taking a measurement, so either ear plugs or specially designed headphones will be used to reduce the noise.

Blood draws

During the blood draws, you may feel a little pain from the needle stick. You might feel light-headed or faint. Later, you might have a bruise, and there is a small risk of infection.

Privacy Risks

The information you provide will be confidential. While we take all precautions to protect your identity, there is always a risk that information could become known to others outside of the study team. This is discussed more fully in the Confidentiality section below.

NEW INFORMATION

You will be told about any new information that might change your decision to be in this study. You may be asked to sign a new consent form if this occurs.

BENEFITS

With your participation in the ultrasound, we would obtain images of your involved joints as well as the typical target joints. With these images, we can establish a baseline of your joint health. We can then compare these current images to future imaging in order to determine whether changes have occurred, whether you are currently having a bleeding episode, synovitis (inflammation of the synovial membrane), or arthritic swelling, all of which require different interventions. We may find that some of your blood tests correlate with these findings; however, there are no direct benefits associated with having extra blood drawn for biomarker testing or for the repository. The results of this study could benefit other people in the future with bleeding disorders.

COSTS

You will not be charged for any tests or procedures that are done only for this study, including ultrasounds, x-rays (first 10 subjects only), MRIs (first 10 subjects only), research blood draws, and testing of research blood samples. We will not cover the cost of clotting factor or routine clinical laboratory tests.

You or your insurance company may be billed for any standard medical care given during the research study, such as clinic visits or routine clinical laboratory tests.

PAYMENT FOR PARTICIPATION

You will be compensated \$150 per visit for your baseline, year 1, year 2, and year 3 visits. In addition, you will be compensated \$150 for both your first acute pain episode visit and your first post-acute pain visit. You will also be compensated up to \$50 per visit for travel for your baseline, year 1, year 2, and year 3 visits, and for your first acute pain episode and your first post-acute pain episode visits.

We encourage and allow you to come in for an evaluation for multiple acute pain episodes and we may include data from those visits in the analysis; however, we will not compensate you for acute pain episode visits or post-acute pain visits beyond the first ones. Additional visits for acute pain episodes will be considered standard medical care.

ALTERNATIVE TREATMENT

This is not a treatment study. Your alternative is to not be in this study.

CONFIDENTIALITY

Your participation in this study will be noted in your medical record. Information from the study will be given to the sponsor. “Sponsor” includes any persons or companies that are contacted by the sponsor to have access to the research information during and after the study.

Your information will be kept confidential. We will assign you a study number. Your data and samples will be coded with the study number, so they will contain no identifying information. We will keep the code that links your name and other identifying information to your data and samples separate from your data and samples. Although we take precautions to protect your confidentiality, absolute confidentiality cannot be guaranteed if we need to give information to the sponsor and there is always a risk that information could become known to others outside the research team.

This study will be registered on clinicaltrials.gov.

AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES

What information may be used and given to others?

The study doctor will get your personal and medical information. For example:

- Past and present medical records
- Research records
- Records about phone calls made as part of this research
- Records about your study visits.

Who may use and give out information about you?

The study doctor and the study staff.

Who might get this information?

- The sponsors of this research, Bloodworks Northwest. Others required by law to review the quality and safety of research, including: the U.S. Food and Drug Administration (FDA), other government agencies in the United States and Western Institutional Review Board® (WIRB®)

Your information may be given to:

- Western Institutional Review Board® (WIRB®)

Why will this information be used and/or given to others?

- to do the research,
- to study the results, and
- to see if the research was done right.

If the results of this study are made public, information that identifies you will not be used.

What if I decide not to give permission to use and give out my health information?

Then you will not be able to be in this research study.

May I review or copy my information?

Yes, but only after the research is over.

May I withdraw or revoke (cancel) my permission?

You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the study doctor. If you withdraw your permission, you will not be able to stay in this study.

This permission will be good until December 31, 2035.

When you withdraw your permission, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others.

Is my health information protected after it has been given to others?

While we are taking every measure to protect your privacy, once we release information, there is a risk that your information will be given to others without your permission.

COMPENSATION FOR INJURY

If you think you have an injury or illness related to this study, contact Dr. Kruse-Jarres at either 206-689-6507 or 206-292-6525 (select option 3) right away. She or one of the other study doctors will treat you or refer you for treatment. No money has been set aside to pay for things like lost wages, lost time, or pain and suffering. However, you do not waive any rights by signing this consent form. Bloodworks Northwest will plan to pay up to \$10,000 to reimburse for out-of-pocket expenses related to the treatment of physical injury or illness resulting from the study.

VOLUNTARY PARTICIPATION AND WITHDRAWAL

Your participation in this study is voluntary. You may decide not to participate or you may leave the study at any time. Your decision will not result in any penalty or loss of benefits to which you are entitled.

Your participation in this study may be stopped at any time by the study doctor or the sponsor without your consent for any reason, including:

- if it is in your best interest
- you do not consent to continue in the study after being told of changes in the research that may affect you

If you leave the study before the planned final visit, you may be asked by the study doctor to have some tests or procedures done so that you leave the study safely.

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.

SOURCE OF FUNDING FOR THE STUDY

Funding for this study is provided by CSL Behring. Drs. Kruse-Jarres, Konkle and Johnsen have been paid consultants for CSL Behring in the past and may be in the future.

QUESTIONS

Contact Research Coordinator Heidi Thiemann, PhD, at 206-689-6234 or Principal Investigator Dr. Rebecca Kruse-Jarres at either 206-689-6507 or 206-292-6525 (select option 3) for any of the following reasons:

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

If you have questions about your rights as a research subject or if you have questions, concerns or complaints about the research, you may contact:

Western Institutional Review Board® (WIRB®)
1019 39th Avenue SE Suite 120
Puyallup, Washington 98374-2115
Telephone: 1-800-562-4789 or 360-252-2500
E-mail: Help@wirb.com

WIRB is a group of people who independently review research.

WIRB will not be able to answer some study-specific questions, such as questions about appointment times. However, you may contact WIRB if the research staff cannot be reached or if you wish to talk to someone other than the research staff.

Do not sign this consent form unless you have had a chance to ask questions and have gotten satisfactory answers.

If you agree to be in this study, you will receive a signed and dated copy of this consent form for your records.

If you agree to provide consent for this study, you are agreeing to allow us to contact you in the future for additional study visits. You may stop your participation at any time.

I agree that blood can be drawn to test for biomarkers.

Yes No Initials _____ Date _____

I agree that my blood can be drawn to store in the repository.

Yes No Initials _____ Date _____

I give permission for researchers to use the blood drawn for the repository for future studies as long as my information is deidentified.

Yes No Initials _____ Date _____

I give permission for researchers at Bloodworks Northwest to share my deidentified data with researchers at other institutions.

Yes No Initials _____ Date _____

CONSENT

I have read this consent form (or it has been read to me). All my questions about the study and my part in it have been answered. I freely consent to be in this research study.

By signing this consent form, I have not given up any of my legal rights.

Consent and Assent Instructions:

*Consent: Subjects 18 years and older must sign on the subject line below
For subjects under 18, consent is provided by the parent or guardian*

Assent:

Written assent is required for subjects aged 16 through 17 years using the Assent section below and the Information Sheet for Children appropriate to their age.

Subject Name (printed)

CONSENT SIGNATURE:

Signature of Subject (18 years and older)

Date

Signature of Parent or Guardian
(when applicable)

Date

ASSENT SECTION:

Statement of person conducting assent discussion:

- I have explained all aspects of the research to the subject to the best of his or her ability to understand.
- I have answered all the questions of the subject relating to this research.
- The subject agrees to be in the research.
- I believe the subject's decision to enroll is voluntary.
- The study doctor and study staff agree to respect the subject's physical or emotional dissent at any time during this research when that dissent pertains to anything being done solely for the purpose of this research.

Statement of Parent or Guardian:

My child appears to understand the research to the best of his or her ability and has agreed to participate.

Signature of Parent or Guardian

Date

Printed Name of Person Conducting the
Informed Consent Discussion

Position

Signature of Person Conducting the
Informed Consent Discussion

Date

ASSENT FORM FOR CHILDREN

Statement to be read to children in the presence of a witness:

Your doctor would like to collect some information about your health from your medical record. Your doctor or nurse might ask you some questions about your health. You do not have to answer any questions you do not want to. If you join the study and sign this form, you will come to clinic at least four times over three years. We will ask you to complete some questionnaires and assessments; take your blood; and take images of your knees, ankles, and elbows with an ultrasound machine. If you are one of the first ten participants in this study, we will also take x-ray and MRI images of your target joint and the joint on the opposite side.

For the ultrasound, there are no known risks but the gel might feel sticky. For the x-rays, there is minimal exposure to radiation. The MRI machine makes loud banging noises and you will lie in a small enclosed area which may feel scary. If you have metal in your body, you won't be able to have MRIs. You might feel a pinch when we draw your blood and your arm might be sore and/or you might have a bruise for a few days.

Your parent said that it would be ok for you to participate in this project but we still would like to know whether or not you want to participate. If you do not want to participate in this project, you will still get the same care that you have been getting. Do you have any questions?

If it is ok with you, your doctor will save any of the blood sample that is left over after the tests in case new tests need done to be later.

Date: _____

Child's name: _____

Signature: _____

Witness: _____

Subject Identification Number: _____