# RESEARCH PARTICIPANT INFORMED CONSENT AND PRIVACY AUTHORIZATION FORM

**Protocol Title**: A Phase 2 Multicenter Randomized Single Arm Crossover Trial Evaluating the Safety and Efficacy of Autologous Volar Fibroblast Injection into the Terminal Limb of Amputees

**Application No.:** IRB00283105

**Sponsor:** Department of Defense (DoD)

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You are being asked to join a research study. Participation in this study is voluntary. Even if you decide to join now, you can change your mind later.

This study is a multi-site study, meaning it will take place at several different locations. Because this is a multi-site study, this informed consent form includes two parts. The first part of this document includes information that applies to all study sites. The second part of the consent form includes information specific to the study site where you are being asked to enroll.

## 1. Research Summary (Key Information):

The information in this section is intended to be an introduction to the study only. Complete details of the study are listed in the sections below. If you are considering participation in the study, the entire document should be discussed with you before you make your final decision. You can ask questions about the study now and at any time in the future.

We are asking you to volunteer for a research study to determine the safety of volar fibroblast (stem cell) injections to the residual limb of people with a below the knee amputation. Volar fibroblast injections may change the skin on your residual limb to be thicker like the skin on the sole of your foot or the palm of your hand. We will use study data to determine if treating the skin with stem cells helps with prosthesis use wearability and comfort in people with a lower limb amputation.

You are being asked to participate in this study because you are between 18-75 years old with a lower limb amputation. If you join the study, you will have a blood test to screen for eligibility. If you qualify, you will have a small portion of your skin biopsied from either the palm of your hand or sole of your foot. The biopsy will be sent to the Johns Hopkins Cell Therapy Lab for processing. Once the cells are prepared, you will have 1 to 3 visits with your doctor to inject the cells. You will then be asked to complete 4 follow-up monitoring visits that involve a physical exam, non-invasive imaging of your skin, and questionnaires. Your participation in this study will last for up to one year.

This is a randomized controlled trial. That means that you will be assigned by chance to receive either stem cell injections or a vehicle control (an injection with no stem cells). You will not be told which group you are assigned until the final study visit. If you are assigned to the control group, you will have the option of getting the stem cell injections after the final study visit. We will pay you up to $500 if you complete all study visits.

There are potential risks involved with having a skin biopsy and the injections. The risks are explained in more detail later in this consent form. If you do not want to accept these risks, you do not have to join the study.

This study is funded by the Department of Defense (DOD) and is being carried out in 4 major treatment facilities across the United States, including three military treatment centers that are taking care of service members who are injured in the line of duty. The Department of Defense (DOD) will have access to records for audit purposes.

## 2. Why is this research being done?

This research is being done to test the safety of volar fibroblast injections. Volar fibroblasts are skin cells from the palm of your hand or sole of your foot. When injected in other areas of the body, these cells can change the features of the skin by making it thicker, like the palm of your hand or sole of your foot. Previous studies have shown that volar fibroblast injections are safe in healthy adults. The goal of this study is to see if volar fibroblast injections are safe in adults with a below the knee amputation. The skin at the end of the residual limb is not meant to withstand the pressure and friction of wearing a prosthetic device. This study is the first step to see if thickening the skin will help improve prosthesis use in people with a below the knee amputation.

***Are there any investigational drugs/devices/procedures?***

The use of autologous skin fibroblasts in this research study is investigational. The word "investigational" means that autologous skin fibroblasts are not approved for marketing by the Food and Drug Administration (FDA). The FDA is allowing the use of autologous skin fibroblasts in this study.

***Who can join this study?***

People who are 18-75 years old with a below the knee amputation who are ambulatory prosthesis users can join the study.

***How many people will be in this study?***

20 people will be enrolled across 4 participating centers.

## 3. What will happen if you join this study?

If you agree to be in this study, we will ask you to do the following things:

- You will come in for a screening visit which will involve a review of your health history and current medication use, a skin exam and limited physical exam, and vital signs.
- If you are female of childbearing potential, you will have a urine pregnancy test. If tests come back positive, you will not be able to participate in the study
- You will have blood drawn (about 2 teaspoons) to test for infectious disease. These tests are done to determine if cells can be processed by the Johns Hopkins Cell Therapy Lab. Your blood sample will be identified by name, medical record and date of birth. If blood tests are positive, you may not be eligible to participate in the study.

- If you are eligible, you will be scheduled for a biopsy visit.
  During this visit, the following things will happen:
  - A small area of skin no larger than the size of the tip of a pencil eraser will be biopsied from either your hand or foot. You will decide which area you prefer. The amount of time for the biopsy is about 20 minutes. The biopsy will be done in the same way in which a clinical biopsy is done. We will inject a local skin numbing medicine. Then we will use a small biopsy instrument (about 4 mm or less than 1/4 inch in diameter) to collect a piece of skin about 2-mm thick. The image below shows the approximate size of the skin biopsy:

    

    After the skin sample is taken, a small stitch and/or dissolvable gel foam will be placed at the site of the biopsy to aid healing. You will be given a biopsy site care information sheet so you know how to care for your biopsy site at home. The skin sample will be sent to the Johns Hopkins Cell Therapy Lab in Baltimore, Maryland for processing. Your skin sample will be identified by name, medical record and date of birth. The cells that will be returned for injection will contain this information.
  - Your doctor will then identify and mark the areas on your residual limb for future monitoring. These sites will also receive injections. These areas will be marked with very small tattoos, the size of a pinpoint or freckle, using tattoo ink.
  - A member of the research team will take non-invasive measures of the skin on your residual limb. They will use a durometer, a hand-held device that looks like a small tire gauge, and place it gently on the skin near the areas for injection to measure how firm the skin is. We will use Optical Coherence Tomography (OCT) to measure the thickness of your skin. The OCT device is a non-invasive instrument used to obtain an image of your skin layers. The OCT uses light to capture two- and three-dimensional images of your skin. The use of this device is not painful and should only feel like pressure against your skin.
  - A member of the research team will take photos of your residual limb to measure the size of existing wounds.

- You will come back in 14 days to have your sutures removed. During this visit, we will also collect vital signs and conduct a skin exam and assessment of adverse events.

- You will then be assigned by chance (like flipping a coin), to either injections with volar fibroblasts or to injections with a vehicle control. You have a 50% chance of being assigned to either group. We are using this method for deciding which group you are assigned because it is not clear if volar fibroblasts are safe and effective. Therefore, we will compare outcomes in people injected with volar fibroblasts to outcomes in people injected with a vehicle control. You will not be informed what group you were assigned until the final follow-up visit.
- If you are assigned to the volar fibroblasts group, you will have 1-3 visits within one week with your doctor who will inject fibroblast cells obtained from your baseline biopsy as follows:
    - We will numb the skin before cell injections. Depending on the size of the injection area, we may use a topical anesthetic (EMLA) and/or a ring block. A ring block is a local anesthetic (1% Lidocaine) that is injected near a nerve to cause a numb sensation for an entire area.
    - Cells will be injected into areas that include those identified on the first visit. Cells will be injected into an area of the residual limb covering up to 25 square centimeters.
    - If you are a female of child-bearing potential, you will take a urine pregnancy test at each injection visit.
    - You will have a limited physical exam, vital signs, and an assessment of adverse events
    - We may assess skin thickness and firmness at these visits using the durometer and the OCT machine.
- If you are assigned to the control group, you will have 1-3 visits within one week with your doctor who will inject cryoprotectant. Cryoprotectant is a liquid which keeps your cells safe from damage while they are frozen and awaiting injection. People in the control group will receive this liquid (cryoprotectant) without the cells inside of it.
    - We will numb the skin before cell injections. Depending on the size of the injection area, we may use a topical anesthetic (EMLA) and/or a ring block. A ring block is a local anesthetic (1% Lidocaine) that is injected near a nerve to cause a numb sensation for an entire area.
    - Cryoprotectant will be injected into areas that include those identified on the first visit. Cryoprotectant will be injected into an area of the residual limb covering up to 25 square centimeters.
    - You will have a limited physical exam, vital signs, and an assessment of adverse events
    - We may assess skin thickness and firmness at these visits using the durometer and the OCT machine.
- No matter which group you are assigned to, you will be asked to return for 4 monitoring visits at 2 weeks, 1, 2 and 3 months following the last injection visit. During these visits the following things will happen:
    - You will have a limited physical exam and a skin examination
    - Vital signs will be taken and there will be an assessment of adverse events
    - A member of the research team will take non-invasive measures of skin firmness and thickness using the durometer and the OCT machine.
    - A member of the research team will take photos of your residual limb to assess wound recurrence and to measure the size of existing wounds.
    - You will be asked to complete surveys that ask about your physical function, pain, prosthesis use, health care services related to your amputation, quality of life, and mood.
- If you are assigned to the control group, you will be offered volar fibroblast injections at the final study visit and you will be followed for an additional 3 months.

**Cell lines:**

Your tissue sample will be used to create a living tissue sample (called a "cell line") that can be grown in the laboratory. This allows researchers to have an unlimited supply of your cells in the future without asking for more samples from you. Each cell contains your complete DNA.

- There is the possibility that your cells or the created cell lines might be used in research that will involve genetic manipulation of the cells or the mixing of human and non-human cells in animal models.
- The cell lines may be shared with researchers both inside and outside of Johns Hopkins, including our commercial partners.
- The cell lines may be used to develop treatments for a variety of diseases and conditions.

**Photographs/Video recordings:**

As part of this research, we are requesting your permission to create and use photographs to help answer the research question. Any photographs taken will not be used for advertising or non-study related purposes.

You should know that:

- You may request that the photography be stopped at any time.
- If you agree to allow the photographs and then change your mind, you may ask us to destroy that imaging. If the imaging has had all identifiers removed, we may not be able to do this.
- We will only use these photographs for the purposes of this research.

**Will research test results be shared with you?**

This study involves research tests that may produce information that could be useful for your clinical care. We will share this information with you.

**How long will you be in the study?**

You will be in this study for up to one year.

## 4. What happens to data and biospecimens that are collected in the study?

If you join this study, your data and biospecimens will be used to answer the research question and your data will be used to publish the findings of this study. Biospecimens may include any of the following: blood, tissue, saliva, urine, bone marrow, cells, etc. Most biospecimens contain DNA, which is the genetic code for each person.

You will not own the data and/or biospecimens collected from you as part of this research study. If researchers use them to create a new product or idea, including those that may have commercial value, you will not benefit financially from those efforts.

This study involves genetic testing on samples that you provide. The Genetic Information Nondiscrimination Act (GINA) is a federal law that helps reduce the risk of discrimination by health insurers or employers based on your genetic information. GINA does not protect you from discrimination if you apply for other types of insurance (such as life, disability or long-term care). GINA also does not protect you against discrimination based on an already-diagnosed genetic condition or disease.

Genetic information is unique to you and your family. Even without your name or other personal identifiers, it may be possible to identify you or other members of your family with your genetic information.

Johns Hopkins follows procedures so that people who work with your DNA information for research cannot discover it belongs to you, unless you have given consent. However, new techniques will likely make it easier to link your genetic data to you in the future, so we cannot promise that your genetic information will never be linked to you.

Johns Hopkins researchers and their collaborators may use the data/biospecimens collected in this study for future research purposes and may share some of the data/biospecimens with others.

Future research may include:

- Genetic research: Study of human DNA to find out what genes and environmental factors contribute to diseases. Each cell contains your complete DNA.
- Gene sequencing: Gene sequencing of your DNA provides researchers with the code to your genetic material
- Cell line creation: Cell lines can be grown in the laboratory. This allows researchers to have an unlimited supply of your cells in the future without asking for more samples from you.

Because science constantly advances, we do not yet know what future use of research data or biospecimens may include. This future research may be unrelated to the current study and may include outside collaborators.

Sharing data and/or biospecimens is part of research and may increase what we can learn from this study. Often, data/biospecimen sharing is required as a condition of funding or for publishing study results. It also is needed to allow other researchers to validate study findings and to come up with new ideas. Your data and/or biospecimens may be shared with researchers at Johns Hopkins and other institutions, for-profit companies, sponsors, government agencies, and other research partners. Your data and/or biospecimens may also be put in government or other databases/repositories.

We (Johns Hopkins) will do our best to protect and maintain your data/biospecimens in a safe way. One of the ways we protect data/biospecimens is by limiting the uses of the information and the type of information that is shared, especially your personal information. This may occur through data/specimen sharing agreements and review by oversight groups within Johns Hopkins.

If data/biospecimens are used or shared with types of information that may be likely to identify, you such as your name, address or medical record number, further institutional review and approval would be required. In these cases, Johns Hopkins will review whether additional consent from you is required. Generally, if your data/biospecimens are used/shared without any personal identifiers or with information that is less likely to identify you (such as the date of a procedure), further review and approval is not needed.

Data/biospecimen sharing could change over time, and may continue after the study ends.

The use and sharing of your data and biospecimens is required for participation in this research study. If you are not comfortable with the use and sharing of your data in future research without further consent, you should not participate in this study. The future use of your biospecimens is optional, and is explained at later in this consent form.

## 5. What are the risks or discomforts of the study?

- **Tattoo markings:** The tattoo markings will be permanent and will have the appearance of a dark freckle. While the markings are being created, the needle we use to apply the tattoo may cause discomfort, like a small pinch or insect bite. In the rare and unusual case where cells fail to grow or are rejected for any reason and are not available for injection, then you will be given the option of a small punch biopsy in those areas of tattooing to remove the marking.
- **Skin Biopsy:** You will have a small amount of pain and may have bleeding at the site of biopsy. There is a very small chance of developing an infection. The biopsy site will leave a small scar when it heals. We will screen carefully for keloids (excess growth of scar tissue), but in rare individuals with no prior keloid history, keloids or excessive scarring may develop at the biopsy site. This risk is increased in people of certain ethnic backgrounds, which can be discussed with the study doctor.
- **Local Anesthesia:** Before the skin biopsies and injections with the study material, the sites may be anesthetized with local anesthesia (lidocaine with epinephrine). The risk associated with the possible use of local anesthesia is very small and is mainly related to minor discomfort (typically a burning sensation), possible bleeding, and a very small chance of infection or allergic reaction (less than 1%).
- **EMLA and Ring Block:** Potential side effects of EMLA are usually mild, go away with time, and include local skin reactions such as swelling, paleness, alterations in temperature sensation, redness, itching, or rash. Some skin darkening at the site of application has rarely been reported. With much larger doses and exposure times than we propose to use here, there are rare reports of severe complications such as allergic reactions. For this reason, we will use a minimal dose and time with supervision in the clinic. Potential risks associated with ring blocks include infection, bleeding, vascular injection of anesthetic, or nerve injury. Amounts of topical and local anesthetic applied and injected will be well below toxic amounts.
- **Stem cell/vehicle control injection:** Due to repeat injections of the study materials with a syringe, discomfort, bleeding, redness, swelling, pigmentation (skin darkening), and bruising may occur at the study drug administration areas. There is a small risk of infection. Cellular injections have been rarely associated with mild redness, swelling, pain, bumps, irritation, skin darkening and itch at the injection site (less than 10%). There may be other symptoms or side effects that we are not yet aware of. For example, we will take your normal cells and grow them in the lab for about 1 month. Though these laboratory grown cells have been routinely used in marketed products for roughly 10 years, unknown risks are possible. A portion of the media in the cell injections (called DMSO) can cause bad breath, hypersensitivity, and skin irritation and/or changes like redness, hives or dryness. Very rarely it can cause blistering or headaches, sedation and nausea. The media can increase the movement of chemicals from outside your skin to inside your skin. So, there is the risk of irritation, sensitivity or other side effects related to the exposed chemical or drug. There is a small risk of anaphylaxis (severe allergic reaction) which might cause **death.**

- **Blood sample:** Taking blood may cause discomfort, bleeding, or bruising where the needle enters the body. In rare cases, it may result in fainting. There is a small risk of infection. Over the duration of the study, you will be asked to provide a blood sample once during screening, a maximum of 15 mL (1 tablespoon).
- **Photographs:** You may be recognizable from the photographs taken during the study. Every effort will be made to make sure that you are not identifiable in these photos, but this might not be possible.
- **Questionnaire:** You may get tired or bored when we are asking you questions or you are completing questionnaires. You do not have to answer any question you do not want to answer.
- **OCT Imaging:** No pain is expected with OCT imaging, but it might be slightly inconvenient to stay still for several minutes during imaging.
- **Durometer:** No pain is expected with Durometer evaluation. The Durometer device will read the skin response under short-term mild pressure from the device.
- **Confidentiality:** There is the risk that information about you may become known to people outside this study.
- **Unknown risk:** There may be side effects and discomforts that are not yet known.

## 6. Are there risks related to pregnancy?

This research may hurt an embryo or fetus in ways we do not currently know. You cannot take part in this study if you are pregnant. It is unknown whether this research may hurt an embryo or fetus.

## 7. Are there benefits to being in the study?

You may or may not benefit from being in this study. Your prosthetic might be easier to wear after graft injections, but this cannot be guaranteed.

If you take part in this study, you may help others in the future.

## 8. What are your options if you do not want to be in the study?

You do not have to join this study. If you do not join, your care will not be affected.

## 9. Will it cost you anything to be in this study?

No.

## 10. Will you be paid if you join this study?

Participants may receive up to a total of $500 for completing the study. The first compensation payment of $150 will be provided after the participant completes the baseline biopsy visit. The remaining $350 compensation will be provided after completing the final monitoring visit. Participants randomized to the control group who proceed with fibroblast injections after completing the three month monitoring visit will receive an additional $350 for completing additional monitoring visits. Participants will be eligible for an additional $20 per milestone visit when traveling at least 50 miles round trip.

**See the site-specific consent information section of this consent for additional information on payments at your study site.**

## 11. Can you leave the study early?

- You can agree to be in the study now and change your mind later.
- If you wish to stop, please tell us right away.
- Leaving this study early will not stop you from getting regular medical care.

If you leave the study early, Johns Hopkins may use or share your health information that it has already collected if the information is needed for this study or any follow-up activities.

Tell your doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor or nurse practitioner if you are thinking about stopping so he/she can evaluate any risks from the study material. Another reason to tell your doctor or nurse practitioner that you are thinking about stopping is to discuss what follow-up care could be most helpful for you.

If you withdraw from the study, the research staff will continue to report any side effects you experience from the study materials. The research staff will continue to report this information for as long as you are followed after graft injections. If you do not want this done, you must specifically tell your study doctor or nurse practitioner.

## 12. Why might we take you out of the study early?

You may be taken out of the study if:

- Staying in the study would be harmful.
- You need treatment not allowed in the study.
- You fail to follow instructions.
- You become pregnant.
- The study is cancelled.
- There may be other reasons to take you out of the study that we do not know at this time.

If you are taken out of the study early, Johns Hopkins may use or give out your health information that it has already collected if the information is needed for this study or any follow-up activities.

## 13. Will the study require any of your other health care providers to share your health information with the researchers of this study?

As a part of this study, the researchers may ask to see your health care records from your other health care providers.

## 14. What other things should you know about this research study?

During the study, we will tell you if we learn any new information that might affect whether you wish to continue to participate.

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. If you would like to review the information for this study, or a summary of the results, ask the study team doctor for the ClinicalTrials.gov study registration number.

During this study, you will not have access to certain medical information and test results collected for study purposes. If an emergency occurs while you are in the study, medical information needed for your treatment can be made available to your study doctor and other physicians who treat you. When the study is completed, all the information in your medical record will be available to you.

**What is the Institutional Review Board (IRB) and how does it protect you?**
This study has been reviewed by an Institutional Review Board (IRB), a group of people that reviews human research studies. The IRB can help you if you have questions about your rights as a research participant or if you have other questions, concerns or complaints about this research study. You may contact the IRB at 410-502-2092 or jhmeirb@jhmi.edu

For this multi-site study, Johns Hopkins has agreed to serve as the single IRB (sIRB) providing oversight for all sites. You may contact the Johns Hopkins IRB at 410-502-2092 or jhmeirb@jhmi.edu with your questions or concerns.

**What should you do if you have questions about the study, or are injured or ill as a result of being in this study?**

Call the principal investigator for your study site, which is listed in the **"Site-specific Consent Information"** (Part 2 of this consent).

If you have an urgent medical problem or think you are injured or ill because of this study, call 911 or go to your local emergency department.

If you wish to contact the lead study principal investigator, Dr. Garza, call 410-502-7546. You may contact the principal investigator by letter. The address is on page one of this consent form. If you cannot reach the principal investigator or wish to talk to someone else, call the IRB office at 410-502-2092.

## 15. Optional Study Components:

This part of the consent form is about optional component(s) of the study that you can choose to take part in or not. You can still take part in the main study even if you say "no" to this/these optional component(s).

**Collection and storage of biospecimens for future research:**
You can decline the collection and storage of biospecimens for future research outside of the current study.

Will you allow us to store and use the biospecimens we collect for this study for use in future research outside of the current study?

**YES** _____
Signature of Participant

**NO** _____
Signature of Participant

**Future Contact**
We would like your permission for our research team to contact you in the future. Please note that your decision below does not prevent other researchers at Johns Hopkins from contacting you about other research.

**Please sign and date your choice below:**

**YES** ☐ _____ _____
Signature of Participant Date

**NO** ☐ _____ _____
Signature of Participant Date