Study Title: Botulinum Toxin to the Flexor Digitorum Brevis versus Corticosteroid for the Treatment of Refractory Plantar Fasciitis: A Randomized-Controlled Trial

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Informed Consent Form

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STUDY SUMMARY

You are being asked to take part in a clinical research study. Before you consider participating in this study, it is important for you to know the risks and benefits. It is important for you to understand why the research is being done and what it will involve. Following the summary, you will be given more detailed information.

- Participation in this research is voluntary. You do not have to be in the study.
- The purpose of the study is to test the efficacy of Botox injections in treating plantar fasciitis compared with corticosteroid injections.
- A group will receive the Botox injection, and the other group will receive the corticosteroid injection. They will both be administered in the foot in the same fashion and will look the same to you.
- The study will involve using information from a recent foot X-ray, physical exam and then either one of the injections. The procedures will be explained in detail later in this consent. Your participation in the study will last about 6 months. Study visits will range from 30 minutes to 1 hour and will consist of the initial injection, a 1-month follow up, a 3-month follow up and then a final 6-month follow up visit.

- There are potential risks resulting from receiving either of the drugs in the injections. There are also risks associated with your condition worsening from failure of the study drugs not improving your condition. There are possible minor and very rare serious side effects, which will be explained in full detail later in the consent.
- There may not be any direct benefit to you for participating in this study. Potential benefits to you or others will be explained later in this consent document.
- If you decide not to take part in the study, you have other options such as continuing with your current treatment plan or talking with a VA clinician about different treatments for plantar fasciitis.

Please take time to read the following information carefully and discuss it with friends, relatives and/or health care professionals, if you wish. Ask the research doctor or staff if there is anything that is not clear or if you would like more information. Take time to decide whether you would like to volunteer to take part in this research study or not.

BACKGROUND AND PURPOSE

You are being asked to take part in this study because you are experiencing heel pain that has failed 6-weeks of standard non-operative treatments and is consistent with plantar fasciitis. Before receiving injection therapy as part of the treatment used for this study, you will be fully evaluated which will include a history and physical exam. This will be evaluating for any pain to the bottom of your heel to specific areas of your heel bone or with certain activities. As part of your standard of care, X-rays of your affected foot will have been taken to assess for any other disease that would suggest a different diagnosis other than plantar fasciitis. If you have had prior Botox injections to the bottom of the heel, any Botox injections within the past 3 months, corticosteroid injections less than 3 months ago, previous surgery involving the plantar fascia, an active workers compensation claim for heel pain, or a diagnosis with anything other than plantar fasciitis at initial visit, you will be excluded from participating in this study. If you are currently undergoing any other treatment specific to the plantar fascia or plan on doing so in the next 6 months, we may also exclude you from participation in this study.

The purpose of the study is to determine if Botox (onabotulinum toxin A, BTX-A) injections to the muscle overlying the plantar fascia are more effective than the standard of care that involves injecting a corticosteroid into the plantar fascia. Botox can cause paralysis or weakness to muscles. Botox is made from a protein in the bacteria Clostridium botulinum. This protein blocks nerve signals that control muscle function. It has been shown that Botox also decreases chemicals glutamate and substance P that

are involved in pain responses. Botox injections have been approved by the US Food and Drug Administration (FDA) and successful in other diseases such as neck spasms, headaches, facial wrinkles, and excessive sweating. Treatment of these diseases are all thought to be successful because of stopping the nerve signals in the muscles that cause these conditions and/or decreasing the chemicals that are involved in pain responses.

The specific muscle that would be studied and injected for this study is the flexor digitorum brevis (FDB muscle) that attaches next to the plantar fascia in your heel. Early research suggests that injecting Botox into the FDB at its most proximal site of origin on the heel bone may be very helpful for treatment of plantar fasciitis. Mildly weakening this muscle may reduce pain and allow people to return to their previous levels of activity. The purpose of this study is to assess if using Botox injection therapy will help decrease pain and help patients return to their previous activity levels as good or better compared to corticosteroid injection therapy in patients suffering from plantar fasciitis. The use of Botox for refractory plantar fasciitis in this study is investigational. An investigational use is one that is not approved by the FDA.

The study will use standard of care methods to assess your plantar fasciitis including a history and physical exam, X-ray imaging, and previous treatment responses. Treatment response to the research injections will be assessed by repeat physical exams, different rating scales and questionnaires. No repeat X-rays are necessary for this study.

This study is being conducted by the United States Department of Veteran Affairs (VA).

NUMBER OF PARTICIPANTS

We expect to enroll 65 veteran participants with plantar fasciitis at the VA Salt Lake City Health Care System (VASLCHCS).

STUDY PROCEDURES

This section is designed to explain what you will be required to do, undergo, and experience if you decide to take part in this study.

The research study you have been asked to take part in will last 6 months once you receive the treatment injection. It is a randomized, single-blinded, comparison study between Botox vs.

Corticosteroid injections. A research trial usually involves comparing different treatments. In this research trial, we want to assess whether Botox injections provide better and more reliable treatment of plantar fasciitis than the current standard of care, corticosteroid injections. In a trial, one group will get one treatment and another group will get a different treatment. In a "randomized trial," people are put in one treatment group or the other by random chance. This means that a computer will decide by chance which group a participant is in, not the doctors running the trial. All participants in this study will have a 50% chance of receiving Botox injections and a 50% chance of receiving corticosteroid injections. You will not know which injection you will receive; however, the study doctor will know what treatment group you are in – this is called a "single-blinded" trial. The doctor needs to know what treatment group you are in because the amount of drug administered is different and the drug injection sites are slightly different, so it is impossible to blind the physician since they must know which drug they are using, so that they can properly and safely inject the correct site.

Here is what will happen throughout the rest of the study if you decide to take part in this study:

First visit: Medical Screening and Eligibility Determination, with possible treatment (1-2 hours)

At the screening visit, the study team determines if you qualify to join the study. At this visit, you will be evaluated to determine your physical diagnosis (whether you have plantar fasciitis and how severe it is) and your current physical symptoms and previous attempted treatments. The following will take place during the screening visit:

1. We will ask you questions about your illness, medical history, surgical history, medication history and past treatments for this illness.
2. We will give you a physical exam (for example, palpate your heel and determine area and level of pain). We will take X-rays of your feet to rule out other conditions unless you have already had an X-ray in the previous 6 months (in that case you do not need another one). This is considered standard of care and your insurance will be billed.
3. We will write down all the medications you are taking, including vitamins and over-the-counter remedies. You will continue to take these medications and over-the-counter remedies throughout the course of the study, and you will not have to stop any of your current treatments if you have additional medical diseases.
4. You will not be eligible to enroll in the study, if you have had a cortisone injection to the heel in the previous 3 months, a previous Botox injection to the heel or any Botox injections within the previous 3 months, or any known allergies to the research drugs. Additional reasons that will

exclude you from participation in this trial include if there is no increase in pain felt when pressure applied to medial calcaneal tubercle, if your X-rays are positive for calcaneal fractures or tumors, if you have had a previous surgery to the plantar fascia, and if you have an active workers compensation claim for plantar fasciitis, an active infection or fever, or are pregnant. You may also be excluded from participation in this study if you are receiving other treatments specific to the plantar fascia or plan on receiving any during the study period. Please discuss any treatments you are receiving for your planta fascia with the study doctor.

5. If you are eligible to enroll in the study, we will then ask if you would like to participate in the research study, where we will discuss the study design, and go over the informed consent in full detail and leave time for questions or concerns.

6. At this point once eligibility and informed consent have been fully discussed and signed, you may receive treatment. Before you receive treatment, we will ask you questions from questionnaires about your pain on a rating scale, and your current physical functional ability.

7. However, if you want more time to think about the study and discuss with family and friends at home, you are welcome to take as much time as you need to decide and may decide to come back to clinic at a later date for your treatment if you decide to do the study. Refer to next step.

Baseline Visit: Treatment administered, if not done so at first visit (about 30 minutes)

Patient has already proven to be eligible to the study and has been explained the research study and its design. Informed consent has been fully discussed at first visit and is brought back signed for this visit if they have not already done so at their last visit.

1. We will take vital signs, including blood pressure, heart rate, temperature, and oxygen % for standard clinic visit.

2. We will ask about medical history and past treatments to confirm no changes have occurred since last visit.

3. We will perform a physical exam and assess for pain on pressure to the medial calcaneal tuberosity.

4. Once eligibility is confirmed again, we will ask you questions from questionnaires about your pain on a rating scale and, on your own, you will fill out a questionnaire sheet about your current physical functional ability in activities of daily living.

5. You will receive your study injection. The dose of Botox is 20 units of BTX-A in 200 µL of saline and the dose of cortisone is 1 mL of Dexamethasone with 2 mL of 1% Lidocaine *OR* 1 mL dexamethasone, 1 mL of 2% lidocaine and 1 mL saline.

1-month follow up: Physical exam and questionnaire assessment

The study doctor will see you back in the clinic for this visit.

1. We will take vital signs, including blood pressure, heart rate, temperature, and oxygen % for standard clinic visit.
2. We will ask about any physical symptoms, or medication side effects you are having.
3. We will perform a physical exam and assess for pain on pressure to the medial calcaneal tuberosity.
4. We will ask you questions from questionnaires about your pain on a rating scale and, on your own, you will fill out a questionnaire sheet about your current physical functional ability in activities of daily living.

3-month & 6-month follow up: Questionnaire assessment

These visits will be performed over the phone with the study staff.

1. We will ask about any physical symptoms, or medication side effects you are having.
2. We will ask you questions from questionnaires about your pain on a rating scale, and your current physical functional ability in activities of daily living.
3. After the last visit, we will summarize your participation in the study, and discuss plans for ongoing clinical care at the VA.

End of Study visit (only completed by participants who prematurely discontinue their participation in the study)

If you do not obtain adequate pain relief with the study-related injection and elect to receive additional corticosteroid injections and/or surgery after discussion with your podiatrist, we will ask you to meet with the study staff over the phone before you receive your additional plantar fascia-related treatments. We will ask about any physical symptoms or medication side effects you are having. We will also ask you

questions from questionnaires about your pain on a rating scale, and your current physical functional ability in activities of daily living. After this visit, your participation in the study will terminate early.

RISKS

There are certain risks that could occur due to study participation. For example:

- You may experience discomfort during physical exam due to the need of assessing your illness and you having pain in particular areas of the heel.
- You may experience discomfort, bruising and bleeding when the injection therapy is administered. Very rarely, a mild infection can occur from having an injection through your skin.
- You have a 50% chance of being assigned to either drug. This means that there is a chance you would not receive the drug that may be the best therapy response in this study.
- It is possible that your condition could worsen during the study. This could be unrelated or related to study participation. Veterans are subject to having a worsening condition with increase or persistent pain. Any treatment necessary to improve physical condition after the study will be offered, or if you decide to withdraw yourself form the study you will still be offered any other necessary treatments to improve your condition.
- Side effects of corticosteroid injection may include facial flushing, pain around the injection site, insomnia, high blood sugar, temporary high blood pressure and skin changes at the injection site like discoloration or thinning of skin. All these side-effects are expected to be temporary.
- Side effects of Botox injection may include pain and swelling at the injection site, headache and/or flu-like symptoms. Serious side effects may include muscle weakness, vision problems, trouble speaking or swallowing, breathing problems, and/or loss of bladder control. Spreading of Botox has been suggested to be dose dependent, and as we are using small doses of Botox in a single distal foot muscle, the likelihood of serious complications from Botox (BTX-A) in this study is extremely low.
- Sometimes people have allergic reactions to drugs. If you have a very bad allergic reaction, you could die. Signs or symptoms of a life-threatening allergic reaction (anaphylaxis) are rashes, breathing difficulties, wheezing, a fast pulse, sudden drops in blood pressure that could make you feel dizzy or lightheaded, swelling around the mouth, throat, or eyes, and sweating.

If you experience any of these or other side effects during the study, you should get medical help and contact the study doctor or study staff.

Loss of confidentiality
The research team will take precautions to safeguard your confidentiality, but it is possible that a breach of confidentiality could occur.

Unforeseeable Risks
In addition to the risks listed above, you could experience a previously unknown risk or side effects.

Reproductive Risks
There are no adequate and well-controlled studies in pregnant women done with Botox. Botox should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

There are no adequate and well-controlled studies in pregnant women done with corticosteroids. Corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

If you become pregnant while taking part in the study, you should immediately inform the research team, because the effects of Botox on a developing fetus are unknown.

BENEFITS

We cannot promise any benefits to you from being in the study. We expect both research drugs to provide some therapeutic relief based on previous studies and standard of care, but nothing is guaranteed, and some patients derive no benefit from either drug. The benefits possible from both these drugs are reduction or elimination in pain and increase in functional ability.

There are possible indirect benefits to this research:

- Results from the study may help doctors understand how Botox and corticosteroids affect individuals with plantar fasciitis. This could help improve future treatment protocols, develop different treatments for plantar fasciitis or design future research with altered protocols that could provide better benefits. However, this would not directly benefit you.

ALTERNATIVE PROCEDURES

You may choose not to participate in this study. If you decide not to take part in the study, there are other choices available to you. These include continuing with your current treatment plan or talking with a VA clinician about different treatments for plantar fasciitis. There are other drugs available for

treatment of plantar fasciitis that are not being used in this study. There are surgical procedures that can be attempted for plantar fasciitis.

MEDICAL TREATMENT OR COMPENSATION FOR INJURY

The VA has the authority to provide medical treatment to participants who are injured by participation in a VA study. If you are injured as a result of being in this study, the VA will provide the necessary medical treatment in accordance with United States federal law. If you want to make a legal claim against the VA or anyone who works for the VA, special laws may apply. The Federal Tort Claims Act (28 U.S.C. 1346(b), 2671-2680) is a federal law that controls when and how a person can bring a claim against the U.S. Government. If you sign this document, you are not giving up your right to make a legal claim against the United States.

CONFIDENTIALITY

Results of this study may be published, but your identity will not appear in any publications. The researchers will keep all research records that identify you private to the extent allowed by law. Records about you will be kept in locked filing cabinets in offices that only the research staff has access to. Study records will be kept in a secure manner and electronic records will be password protected on encrypted computers. Only people working on the study will have access to your research information. We will do everything we can to keep the study records private but cannot guarantee this.

Your information and the data collected in this study will only be used for the present study and will not be used for future research studies.

We will do everything we can to keep others from learning about your participation in the research.

The VA Institutional Review Board (IRB) is responsible for making sure that researchers follow United States federal laws protecting human subjects who are participating in research studies. Staff from the VA may look at any research records, to make sure the research staff is following the laws that protect you. Representatives from the FDA or the Drug manufacturer of Botox and Corticosteroids may also inspect the research records that identify you.

A description of this research study will be available on *http://www.ClinicalTrials.gov*, as required by U.S. Law. This website will not include information that can identify you. At most, the website will

include a summary of the results. You can search this website at any time (ClinicalTrials.gov ID: NCT05367271).

RIGHT OF INVESTIGATOR TO WITHDRAW

The investigator can withdraw you from the study without your approval. Possible reasons for withdrawal include the inability to comply with the study protocol, worsening of your condition that requires alternative treatment to maintain patient safety, or if the study doctor feels that the study medication is making your condition worse.

COSTS TO PARTICIPANTS AND COMPENSATION

A veteran research participant will not be required to pay for care and services (treatment) received as a participant in a VA research project. However, some veterans are required to pay co-payments for medical care and services provided by the VA. These co-payment requirements will continue to apply to medical care and services provided by the VA that are not part of this study but are considered "standard of care". The initial consult, physical exam, X-rays, conservative treatments, and 1-month follow up visits are considered "standard of care" and you will be required to pay co-payments, if applicable to you. The research visit during which you will receive the injection, the 3-month and 6-month follow up visits and the study medication itself will be provided to you at no cost.

After attending all study visits, you will receive compensation for your time as outlined below. This will be in form of a check which will be mailed to you after study completion by Western Institute of Veterans Research (WIVR).

Study Visit #	Screening/Injection visit	1	2	3	Total
Visit Compensation ($)	0	0	0	50*	
				Total Compensation ($)	50*

***You must complete the entire duration of the study to receive compensation. However, if you terminate your study participation early for additional plantar fasciitis-related treatments AND complete an End of Study visit, you will still be compensated for your participation in the study.**

NEW INFORMATION

Sometimes during the course of a research study, new information becomes available about the treatment that is being studied. If new information about BTX-A or Dexamethasone becomes available during the study, a research doctor will inform you in a timely manner and discuss with you whether this new information changes your decision to continue participating in the study.

If you decide to withdraw at that time or at any time during the research, your research doctor will make arrangements for your medical care to continue. If you decide to continue in the study, you will be asked to sign an updated consent form. Also, after receiving new information about BTX-A or Dexamethasone, your research doctor might decide it is in your best interests to withdraw you from the study. If that happens, the doctor will explain the reasons to you, and make referrals for your medical care to continue.

During the study, we may learn something about your health that could help you and your doctors make decisions about your healthcare. If this happens, we will tell you about these results. We will contact you and make arrangements to discuss this with you.

VOLUNTARY PARTICIPATION

It is up to you to decide whether or not to take part in this study. If you decide to take part you are still free to withdraw at any time, and without giving a reason. Refusal to participate or the decision to withdraw from this study will involve no penalty or loss of benefits to which you are otherwise entitled. If you decide not to take part, you will still receive all standard care that is available to you. This will not affect the relationship you have with your doctor or other VA staff members, nor decrease the standard of care that you receive as a patient. If you want to stop being in this study, please let the research doctor know. That way you can find out what should be done about your routine care outside of the study.

PERSON TO CONTACT

If you have questions, complaints, or concerns about this study, or if you think you may have been injured from being in this study, you can contact Dr. Mikol Anderson at 801-582-1565 ext. 4538. You can also telephone the Study Coordinator Monday through Friday between the hours of 8:00 AM and 4:00 PM at 801-582-1565 ext. 4538.

INSTITUTIONAL REVIEW BOARD

Contact the University of Utah Institutional Review Board (IRB) if you have questions regarding your rights as a research participant. Also, contact the IRB if you have questions, complaints or concerns which you do not feel you can discuss with the investigator. The University of Utah IRB may be reached by phone at 801-581-3655 or by e-mail at irb@hsc.utah.edu, or by U.S. Mail at: 75 South 2000 East, Room 111, Salt Lake City, UT 84112.

HEALTH INFORMATION PORTABILITY AND ACCOUNTABILITY ACT (HIPAA)

There are rules to protect your private health information. Federal and state laws and the federal medical law, known as the HIPAA Privacy Rule, also protect your privacy. By signing this form, you provide your permission called your 'authorization,' for the use and disclosure of information protected by the HIPAA Privacy Rule.

The research team working on the study will collect information about you. This includes things learned from the procedures described in this consent form. They may also collect other information including your name, address, social security number, date of birth, and information from your medical records such as medical history, allergies, X-ray images, clinical assessments, medications, vital signs and any relevant information that is necessary to safely conduct the study.

The research team may also need to disclose your health information and the information it collects to others as part of the study progress. Others may include; Western Institute for Veterans Research (WIVR), Institutional Review Board (ERICA), VA Office of Research and Development, Food and Drug Administration (FDA), Office of Human Research Protections (OHRP), the VA Office of Research Oversight (ORO), and the Government Accountability (GAO).

Your health information disclosed pursuant to this authorization may no longer be protected by Federal laws or regulations and may be subject to re-disclosure by the recipient.

You can revoke this authorization, in writing, at any time. To revoke your authorization, you must write to the Release of Information Office at this facility or you can ask a member of the research team to give you a form to revoke the authorization. Your request will be valid when the Release of Information Office receives it. If you revoke this authorization, you will not be able to continue to participate in the study. This will not affect your rights as a VHA patient to treatment or benefit outside of the study.

If you revoke this authorization, Dr. Mikol Anderson and his or her research team can continue to use information about you that was collected before receipt of the revocation. The research team will not collect information about you after you revoke the authorization.

Treatment, payment or enrollment/eligibility for benefits cannot be conditioned on you signing this authorization. This authorization will expire at the end of the research study unless revoked prior to that time.

INFORMED CONSENT STATEMENT AND AUTHORIZATION

I confirm that I have read this consent document and have had the opportunity to ask questions. All my questions have been answered to my satisfaction. I understand I will be given a signed copy of the consent form to keep. I voluntarily agree to participate in this research study as you have explained in this document.

I authorize the collection, use, and disclosure of my health information in accordance with this form.

_____ Printed Name of Participant	_____ Signature of Participant	_____ Date
_____ Printed Name of Person Obtaining Consent	_____ Signature of Person Obtaining Consent	_____ Date