The Effect of Abobotulinum Toxin A on the Symptoms of Raynaud's Phenomenon, a Double-Blind Randomized Placebo-Controlled Trial

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PROTOCOL TITLE:

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1.0 Objectives*

1.1 This study aims to investigate the effect of abobotulinum toxin A on the symptoms of Raynaud's phenomenon. By studying the effect of abobotulinum toxin A on Raynaud's symptoms among a more diverse population we hope to provide insight into the patients most likely to benefit from abobotulinum toxin A.

1.2 Our hypothesis is that hands that receive injections of abobotulinum toxin A will experience greater relief from symptoms compared to hands which do not

2.0 Background*

2.1 Raynaud's phenomenon affects up to 20% of the population, and is commonly associated with many autoimmune and inflammatory diseases.[1] It affects over 90% of scleroderma patients, but also affects over 10% of patients with systemic lupus, dermatomyositis, rheumatoid arthritis, and primary Sjögren's syndrome.[2] Additionally, Raynaud's phenomenon associated with an immunological disease is commonly has severe progression and can lead to amputation of the affected digits.[2] Symptoms of Raynaud's phenomenon are a result of worsened circulation to the extremities, particularly in the hands. A decrease in circulation leads to ischemia of the tissues, causing pain and functional limitations as well as ulcers and gangrene.[3] This can prove extremely debilitating to patients, reducing quality of life. Treatment options include medications which seek to increase vasodilation, most commonly calcium channel blockers.[4] If patients fail to improve under pharmacological interventions, surgery is often required to alleviate symptoms or remove ischemic and gangrenous tissue.[5] However, studies have shown that botulinum toxin (BoNT) reduces symptoms in certain patient populations with Raynaud's phenomenon.[6-9]

2.2 BoNT works as a vasodilator by blocking the release of neurotransmitters and thereby decreasing the muscular sympathetic response.[10] Therefore, the muscle relaxes and in the case of vascular muscle, allows for vasodilation of the blood vessel. Although approved by the FDA to treat muscle spasms, the specific use of BoNT for the treatment of Raynaud's phenomenon is not recognized.[11] Despite its off-label use, multiple studies support the benefits of using BoNT as a treatment for Raynaud's phenomenon.[12]

2.3 A 2014 study by Neumeister and colleagues shows BoNT improves blood flow in the hand as well as reduces pain and improves function.[7] However, studies have focused on specific patient populations, such as that of scleroderma or systemic sclerosis.[6,13] Additionally, studies have lacked a coordinated methodology with some lacking double-blind experimentation, a control group, or appropriate treatment dosage. Our prospective double-blind

randomized control trial seeks to compare a single formulation of BoNT, aboboutlinum toxin A (Dysport), to a placebo saline group, studying the effect of BoNT on Raynaud's symptoms among a more diverse population to provide insight into the patients most likely to benefit from BoNT. Additionally, we hope that if we have positive findings that this data could be used to justify insurance coverage of BoNT in Raynaud's phenomenon. With BoNT costing hundreds to thousands of dollars per treatment, it can prove a financial burden for patients relying on BoNT for relief from symptoms and prevention of amputation.[14] Preliminary findings from this study could be used to justify further studies for a new indication for Raynaud's phenomenon thus improving patients' chances for coverage and ease of access.

3.0 Inclusion and Exclusion Criteria*

3.1 For this study, patients at UCF Health will be screened in person for eligibility using the following inclusion criteria listed in 3.2. Screening will be performed by Dr. Weinstein or Dr. Sami. (See attached "Eligibility Screening")

3.2 Screening Criteria

- Inclusion Criteria:
    - Male or female adult between 18 and 80 years of age
    - Must have health insurance
    - Must have a current diagnosis of Raynaud's phenomenon
- Exclusion Criteria:
    - Allergy to abobotulinum toxin A or its components
    - Diagnosis of myasthenia gravis
    - Previously received abobotulinum toxin vaccine
    - Previously undergone upper extremity vascular surgery (including surgical sympathectomy)
    - Currently receiving aminoglycoside antibiotics
    - Received abobotulinum toxin A treatment in either hand in the past 6 months
    - Pregnant women
    - Women currently breastfeeding
    - Current tobacco smoker (use in the past 12 months)
    - Unable to read and speak English

- Adults unable to consent
- Individuals who are not yet adults (infants, children, teenagers)Prisoners

4.0 Study-Wide Number of Subjects*

4.1 We plan on enrolling 20 subjects with the aim to accrue 16 subjects who successful screen for eligibility for the study. This number was derived from a power analysis performed with Bee Nash.

5.0 Study-Wide Recruitment Methods*

5.1 Not applicable. This is not a multicenter research study and research will only be conducted at UCF Health clinics in Lake Nona. Local recruitment methods are described in section 19.0 Setting.

6.0 Multi-Site Research*

6.1 Not applicable. This is not a multi-site research project. Research will only be conducted at the UCF Health clinic in Lake Nona.

7.0 Study Timelines*

7.1 Subjects are expected to participate in this study for a total of twelve months. During these twelve months, subjects will be required to come to UCF Health Clinic at 9975 Tavistock Lakes Blvd., Orlando, FL 32827 for a total of five appointments:

- Baseline appointment: 1 hour
- 48-hours follow-up phone call: 5 minutes
- 1-month follow-up appointment: 15 minutes
- 3-month follow-up appointment: 15 minutes
- 6-month follow-up appointment: 15 minutes
- 12-month follow-up appointment: 15 minutes
- For the first 3 months subjects will be asked to complete a weekly survey either online or on paper to bring in.
- For the final 9 months subjects will be asked to complete a monthly survey either online or on paper to bring in.
- Ten months is the anticipated length of time to recruit participants.
- The study is expected to be completed by October 2019.

8.0 Study Endpoints*

8.1 Primary endpoints: Participation in the study will end 12 months after the baseline visit or if the patient elects to be removed from the study, whichever comes first.

8.2 Primary and secondary safety endpoints: adverse reaction to the abobotulinum toxin A solution. If a participant develops a reaction, he or she will be given the option to withdraw but will not be required to withdraw, unless life threatening.

9.0 Procedures Involved*

9.1 Our study is a double-blind randomized placebo-controlled trial.

- Treatment arm: Injection of 300 units of abobotulinum toxin A in 10 ml of non-bacteriostatic normal saline to chosen hand.
- Control arm: Injection of 10 ml of non-bacteriostatic normal saline to chosen hand.
- Randomization will be determined by coin flip as follows:
    - Heads: Right hand – treatment arm; Left hand – control arm.
    - Tails: Right hand – control arm; Left hand – treatment arm.

9.2 Timeline

- Subject visits
    - The abobotulinum toxin A solution and saline solution will be prepared the same day as the subject's baseline visit
    - Baseline Visit
        a. Minute 00-20:
            i. Screening and consent process in screening room
        b. Minute 20-40:
            i. Assessment of baseline Raynaud's symptoms via Baseline Case Report (attached) and photographs will be taken of both hands
            ii. Administration of abobotulinum toxin A solution and normal saline solution
        c. Minute 40-60:
            i. Review post-procedure instructions and how to complete Brief Follow-up Case Reports. Observe subject for any adverse reaction.
    - 48-hour follow-up phone call:

a. Minute 0-5:
    i. Brief phone call to assess for any adverse reactions.

- 1-month (+/- 8 days) Follow-up
    a. Minute 00-15:
        i. Assessment of Raynaud's symptoms via Follow-up Case Report (attached) and photographs will be taken of both hands
- 3-month (+/- 15 days) Follow-up
    a. Minute 00-15:
        i. Assessment of Raynaud's symptoms via Follow-up Case Report (attached)
- 6-month (+/- 15 days) Follow-up
    a. Minute 00-15:
        i. Assessment of Raynaud's symptoms via Follow-up Case Report (attached) and photographs will be taken of both hands
- 12-month (+/- 15 days) Follow-up
    a. Minute 00-15:
        i. Assessment of Raynaud's symptoms via Follow-up Case Report (attached) and photographs will be taken of both hands

- Subject surveys
    - Months 0-3:
        a. Every week the subjects will be asked to complete the Brief Follow-up Case Report either online or on a paper version given to the subject.
    - Months 4-12
        a. Every month the subjects will be asked to complete the Brief Follow-up Case Report either online or on a paper version given to the subject
- Solution preparation

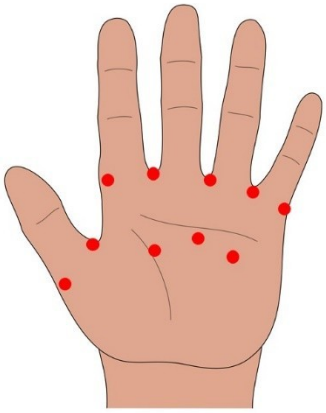
- 300 unit vials of abobotulium toxin A will be reconstituted with 10 ml of non-bacteriostatic normal saline yielding a final concentration of 30 units per 1 ml.
- The solutions will be drawn up in 1 cc syringes utilizing a 25g needle by Dr. Weinstein. The needle with then be replaced with a capped 30g ½ inch needle.
- All solutions will be prepared and drawn up by Dr. David Weinstein the day of use after consent has been obtained and discarded immediately after use.
- The syringes will be labeled with a red or blue label for randomization by Amelia Winter, Samantha Prabakaran, or Dr. Naveed Sami.

• Screening and consent:

- Each participant will sit down with the principal investigator to discuss the study in depth and review the screening criteria. After all risks, benefits, alternatives, and questions have been discussed consent will be obtained.
- After the informed consent form is signed, the eligibility screening portion of the case report form will be filled out by the principal investigator with the research subject. If necessary, a pregnancy test will be performed.

• Administration of study solution:

- 10 sites on each palm will be used (see image below):
    a. Two at the base of the thumb
    b. Three in the middle of the palm
    c. Five at the proximal base between each finger



- The participants' sites of administration will be cleansed with isopropyl alcohol before administration. Needles will be introduced at a 90-degree angle subcutaneously. 1 ml of solution will be injected per site.
- A board-certified dermatologist, Dr. Weinstein, will be administering all solutions to minimize risks for participants.
- Subjects will be given the clinic number and asked to call if they think they are experiencing any adverse effects.
- Subjects will be evaluated either in person or over the phone 1 month and 3 months after treatment.

• Disposal protocol:

- After use, needles will be disposed of in red harps container according to UCF Health policy.
- After use, urine samples will be disposed of in the toilet according to UCF Health policy.

9.3

• Risk Management:

- Participants will be directly observed during the administration of the botulinum toxin and placebo for any adverse events. An anaphylaxis kit is available in clinic should any participant experience such an event. The principal investigator is certified in basic cardiopulmonary life support and an AED is present in the facility. Participants will be provided with the phone number of the

PI should any issues related to participation in the study arise.

- Abobotulinum toxin A is the only drug used in this research study. It is currently FDA-approved for cervical dystonia, moderate to severe glabellar lines, upper limb spasticity, and lower limb spasticity.
- The following are the source documents (see attached):
    a. Subject ID Assignment Log
    b. Screening and Enrollment Log
    c. Drug Accountability Log
    d. Eligibility Form
    e. Demographics Form
    f. Medical History Form
    g. Baseline Case Report Form
    h. Follow Up Case Report Form
    i. Brief Follow Up Case Report Form
    j. Adverse Event Form

9.4 Data to be collected

- Age
- Gender
- Race
- Ethnicity
- Medical History
    - Past Medical and Surgical History
    - Medications
    - Allergies
    - Social History
        a. Tobacco use
        b. Alcohol use
- Duration of Raynaud's phenomenon
- Visual Analog Scale for Pain (VAS Pain)
- Raynaud's Condition Score (RCS)

- The Disabilities of the Arm, Shoulder and Hand Score (QuickDASH)
- Number of digital ulcers
- Number of attacks/episodes per week
- Photographs of both hands will be taken during every subject visit and will be stored directly in the password protected HIPAA compliant network drive for clinical research at UCF Health. Though the photos will not contain any identifiers, subjects are potentially identifiable from the photos and thus they will be stored in the password protected HIPAA compliant network drive for clinical research at UCF Health.

10.0 Data and Specimen Banking*

10.1 There will be no data or specimen banking for future use.

11.0 Data Management* and Confidentiality

11.1 The data will be analyzed for significant differences with aid of a statistician. A significance level of 0.05 will be used for statistical hypothesis testing. The results of the data analysis will be graphed for each parameter.

- Categorical variables, such as sex (male and female), age, and comorbidities (e.g., scleroderma) will be reported descriptively, as frequencies and percentages. Outcomes in this study are visual analog scale for pain (VAS Pain), Raynaud's Condition Score (RCS), and the Disabilities of the Arm, Shoulder and Hand Score (QuickDASH), which are continuous variables. In addition, the number of digital ulcers and number of attacks/episodes per week, which are discrete variables, will measured as outcomes. These continuous and discrete variables will be expressed as mean ± standard deviation, with standard error of the mean (SEM).
- To assess between group differences, an Independent samples t-tests will be conducted separately for the three time periods: baseline, 1-month, and 3-month. Additionally, a dependent sample t-test will be used to assess within-group differences from 1-month to 3-month, separately for the experimental and control groups. It is possible to use the baseline measurement as a covariate in an analysis of covariance (ANCOVA) and/or in a repeated measures ANOVA. Thus, the researchers will also explore these additional analyses if the sample size permits.
- All tests will be two-sided, and p-values < 0.05 will be considered statistically significant. Statistical analyses will be conducted using SPSS 24.0 (IBM; Chicago, IL).

11.2 Utilizing the statistical software G*Power it was determined that 16 patients would be needed to detect a 2-point difference in the RCS among the treatment arms. (G*Power) This assumes a standard deviation of 1.92, power of 0.8, alpha of 0.05, and effect size (d) of 1.04. (Merkel)

11.3 Data will be managed as follows:

- Data will be stored in the secure HIPAA-compliant database called REDCap.
- Unique identifiers will be created using sequential numbers (i.e. 1, 2, 4 etc.).
- No data collection instrument in REDCap will contain identifying information
- The Screening and Enrollment Log, Drug Accountability Log, Eligibility Forms, Demographics Forms, Medical History Forms, Baseline Case Report Forms, Follow Up Case Report Forms, Brief Follow Up Case Report Forms. Adverse Event Forms (see attached documents) will all be stored in the regulatory binder in a locked drawer in a locked room at UCF Health. Only Dr. David Weinstein will have access to this locked drawer.
- Photographs will be taken with a UCF Health digital camera. The photographs will then be transferred to a folder on a password protected HIPAA compliant network drive for clinical reserach at UCF Health. After transfer of photographs to clinical research folder they will be deleted from the camera. Photographs will be labeled with subject ID number and visits number (i.e Subject 01 3-month)
- A subject ID assignment list (see attached document "Subject ID Assignment List") that links the subject name and contact information with their unique identifier will be stored in a separate folder in locked drawer in a locked room at UCF Health. Only Dr. David Weinstein will have access to this locked drawer.
- Identifying information such as the "Subject ID Assignment List" will only be accessed by the PI and co-PIs for initial entry. It is possible the identifiable information may be referenced if questionable data are detected during data analysis (e.g.: number out of range, missing data).
- The "Screening and Enrollment Log" and the "Subject ID assignment List" will both be disposed of in a HIPAA-compliant shred bin at the completion of the study.
- Informed consents and HIPAA authorizations will be stored in locked drawer in a locked room at UCF Health and kept for a minimum of six years after the conclusion of the study (per UCF data retention policies.)

- Only de-identified data will be used and exported for analysis.
- De-identified data and photographs will be stored for a minimum of five years after the conclusion of the study (per UCF data retention policies).

12.0 Provisions to Monitor the Data to Ensure the Safety of Subjects*

12.1 The plan to periodically evaluate the data collected regarding both harms and benefits to determine whether subjects remain safe is as follows:

- The principal investigator and statistician will review cumulative VAS Pain scores, RCS data, QuickDASH, number of digital ulcers, and number of attacks/episodes per week data at the halfway point (8 subjects).
- If any of the change in VAS Pain scores, RCS, QuickDASH, number of digital ulcers, or number of attacks/episodes per week for the treatment should become statistically significantly worse than the control with a $p < 0.05$ then the study will be suspended immediately.
- Alternatively, if the change in VAS Pain scores, RCS, QuickDASH, number of digital ulcers and number of attacks/episodes per week for the treatment should become statistically significantly better than the control with a $p < 0.05$ then the study will also be suspended immediately.

13.0 Withdrawal of Subjects*

13.1 Subjects will be withdrawn from the research without their consent if they become intolerant to the treatment and/or the researchers determine that they are too nervous, anxious to continue.

13.2 Orderly termination will proceed at the end of study period for all subjects. This will simply mean no further visits and no further data collection will occur.

13.3 Subjects may voluntarily terminate their participation in the research at any time by informing a member of the research team. A subject may partially withdraw from the study after the initial treatment and control have been administered or even during administration if the participant is unable or unwilling to continue or do the follow up visits.

If a subject withdraws or is withdrawn from the study prior to completion, further data collection will be stopped. However, partial data already collected will be used for analysis.

14.0 Risks to Subjects*

14.1 There is no major anticipated risk associated with the study. However potential risks to the subject include:

- Discomfort and pain upon injection and infiltration of abobotulinum toxin A or normal saline
- Temporary muscle weakness that may last 6 weeks
- Negligible bleeding or bruising

- Minimal risk of infection (<1%)[16]
- Allergy to abobotulinum toxin A solution (<1%)
- Furthermore, true allergy to abobotulinum toxin A is extremely rare.[17]

15.0 Potential Benefits to Subjects*

15.1 Potential benefits are not guaranteed to subjects but include:

- Relief from Raynaud's phenomenon symptoms
- Free treatment for their Raynaud's phenomenon

16.0 Vulnerable Populations*

16.1 This study does not involve individual who are vulnerable to coercion or undue influence.

17.0 Community-Based Participatory Research*

17.1 This is not community-based participatory research.

18.0 Sharing of Results with Subjects*

18.1 There are no plans to share results with participants.

19.0 Setting

19.1 Research will be conducted at UCF Health:

- Potential subjects will be identified and recruited at both the UCF Health clinic in Lake Nona and the UCF Health clinic on Quadrangle Blvd.
- Screening, enrollment, initial/baseline study, and follow up study visits will take place at the UCF Health clinic in Lake Nona.
- There will not be a community advisory board.

20.0 Resources Available

20.1 Dr. Weinstein has significant prior experience conducting research, knowledge of the regulations and customs at UCF Health, and works regularly with patients performing dermatologic surgery. All injections will be administered by Dr. Weinstein. Dr. Sami has extensive experience conducting clinical research. In addition, the medical students involved in the project will be able to help significantly. Through the FIRE project Bee Nash will be able to assist with data analysis.

20.2 Resources available to conduct research:

- The study's small sample size of 20 subjects to be enrolled in order to have 16 subjects complete the study makes it likely that the required number of participants will be recruited in less than 8 months. Drs. Weinstein and Sami see at least this number of patients with Raynaud's phenomenon annually. In addition, the rheumatologists at UCF Health see at 3 to 4

times as many patients with Raynaud's phenomenon. Finally, recruiting through the local dermatology society and advertising should supplement the numbers needed to complete the study.

- Research will be conducted during Dr. Weinstein's administrative time or on the weekend.
- The study will be conducted at the UCF Health Clinic, see section 19. Setting.
- While the chances of a research related injury are extremely rare, participants will be required to have health insurance in order to participate in this study. Treatment for research related injury will be made available, however costs associated with this treatment will be billed to the participant's insurance company. Costs not covered by participant's insurance company will be the subject's responsibility. (see Consent Form attached)
- All individuals assisting in the research study will be provided a copy of the IRB-approved protocol and given the opportunity to meet with the principal investigator before recruitment begins. The principal investigator, Dr. Weinstein, will be responsible for informing all research staff of their research-related duties during a personal meeting or via phone or email. The contact information of the principal investigator and co-principal investigator will be distributed to all research staff and the subjects.

21.0 Prior Approvals

21.1 Approval from the medical director and the HIPAA privacy officer of UCF Health will be obtained prior to commencing research.

22.0 Recruitment Methods

22.1 The research team will start recruitment shortly after IRB approval and the abobotulinum toxin A has been received. Patients with a diagnosis of Raynaud's phenomenon will be recruited from the UCF Health Clinic during a patient's visit (medical records will not be searched for patients with a diagnosis of Raynaud's phenomenon) and through advertising on the UCF Health website and within the UCF Health clinic.

22.2 The primary source of subjects will be patients at the UCF Health Clinic and people in the greater Orlando area. This represents a large pool of potential subjects from which to recruit.

22.3 Dr. Weinstein and Dr. Sami will rely on prior labs, pathology reports, and physical examination to determine if the participant has a diagnosis of Raynaud's phenomenon.

22.4 An e-mail and within clinic advertisement may be used to recruit patients (see attached Advertisements). This is a small paragraph describing the study. This text may be displayed in the UCF Health clinic, to other providers at UCF Health or members of the local dermatology society. In addition, a similar small

paragraph describing the study will be posted on the UCF Health website (see attached Advertisements).

22.5 Participants will not be compensated for their time.

23.0 Local Number of Subjects

23.1 We plan to enroll approximately 20 subjects.

23.2 We anticipate most subjects that enrolled to be successfully screened. There may be a few subjects that will fail screening due to failing urine pregnancy testing. Given this, it may be that 18 to 20 subjects need to be enrolled and screened to obtain 16 eligible subjects.

24.0 Provisions to Protect the Privacy Interests of Subjects

24.1 Subjects will be in the same general vicinity during study and will be recruited from UCF Health Clinic. Therefore, there will be the possibility that participants may know and recognize each other.

24.2 Prior to enrollment subjects will be made aware of this possibility and if unacceptable, will be given the option to decline to participate.

24.3 All investigators will have access to all of the information collected on the subjects. The "Subject ID Assignment Log" will be kept in a separate folder so that investigators will only have access to identifiable information if needed for data entry or if there is a data discrepancy. Only de-identified data will be exported and used for data analysis.

25.0 Compensation for Research-Related Injury

25.1 While the chances of a research related injury are extremely rare, participants will be required to have health insurance in order to participate in this study. Treatment for research related injury will be made available, however costs associated with this treatment will be billed to the participant's insurance company. Costs not covered by participant's insurance company will be the participant's responsibility.

26.0 Economic Burden to Subjects

26.1 Subjects have to give his or her time (approximately 2.5 hours) and bear any transportation costs (gas, tolls, etc.). If the subject's health insurance does not cover the costs for treatment related injury, the subjects will be billed for the treatment. There are no other expected costs that subjects will incur as a result of participating in the study.

27.0 Consent Process

27.1 Consent process:

- The consent process will take place in person at the UCF Health clinic in Lake Nona.
- Subjects will be given the option of picking up the consent and HIPAA authorization prior to participation to discuss with their primary care physician, significant other, etc., to help minimize the possibility of coercion or undue influence. Subjects will be able to wait however long they desire after obtaining the study information and before signing the consent and HIPAA authorization. However, if the study is completed before the subject chooses to sign the consent then they will not be allowed to participate.
- Subjects may voluntarily terminate their participation in the research at any time by informing a member of the research team. Other than the initial informed consent no other formal process will be done to document ongoing consent.
- The UCF "SOP: Informed Consent Process for Research (HRP-090)" will be followed.
- The consent process and HIPAA authorization will be documented in writing. The investigator will describe the details of the study and answer any questions the subject may have about the study. Subjects will be given an informed consent and HIPAA authorization for the study and the primary investigator's contact information. Those subjects who express interest in the study will be required to sign the Informed Consent form and HIPAA authorization to ensure that there is no coercion in the study.

28.0 Process to Document Consent in Writing

28.1 The UCF "SOP: Written Documentation of Consent (HRP-091)" will be followed.

28.2 All participants will be required to complete and sign the informed written consent document (see attached) to ensure that there is no coercion in the study. The informed consent documents will be signed both by the participant and by the principal investigator (see attached "Informed Consent").

29.0 Drugs or Devices

29.1 Abobotulinum toxin A being used will be stored in bag label "For Research" in a locked medication refrigerator in a locked room at the UCF Health clinic in Lake Nona. This will only be accessible by authorized study personal. The medication will only be used on research subjects by authorized study personnel. Logging of the drug inventory and administration will be kept on the Drug Accountability Log (see attached).

29.2 The abobotulinum toxin A and normal saline solutions are not investigational drugs and are readily available FDA-approved medications.

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