Study Protocol- Including Statistical Analysis Plan

Title: Miradry Treatment for Focal Axillary Hyperhidrosis (MiraDry Tx)

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# JHM IRB - eForm A – Protocol

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1. **Abstract**
    a. **Provide no more than a one page research abstract briefly stating the problem, the research hypothesis, and the importance of the research.**

Primary hyperhidrosis is a pathological condition characterized by the idiopathic and excessive secretion of sweat beyond normal physiological demand and is localized at particular foci such as the face, axilla, palms of the hands, and soles of the feet. Patients seeking medical attention for hyperhidrosis often report disruptions to their professional and/or social lives due to sweating and subsequently experience many psychosocial difficulties, such as anxiety, social phobia, and depression. Therefore, a psychiatric explanation of causality is frequently offered for these patients during diagnosis. Excessive sweating is often mistakenly interpreted as a symptom of an anxiety disorder and can be cause for social embarrassment, exacerbating emotional stress and social avoidance. As currently constituted, the treatment of secondary psychosocial symptoms in primary hyperhidrosis is poorly understood and requires further investigation. We have previously collected data which showed substantial improvement in quality-of-life and psychometric evaluation of primary hyperhidrosis patients after surgical intervention. These data suggest the profoundly beneficial potential of medical treatments in terms of psychosocial deficits that were previously deemed primarily psychological. This study aims to evaluate the efficacy of miraDry ® a novel non-invasive treatment system for primary hyperhidrosis of the axillae. This study hypothesizes a similar finding in the miraDry ® system as was observed for the surgical modality. If this prospective study finds a significant improvement in psychometric evaluation scores after miraDry ® treatment, then it would strongly suggest that patients seeking medical intervention to alleviate excessive sweating should experience marked improvement not only in their levels of sweating, but also in the psychopathological symptoms that they experienced pre-treatment. These findings could result in substantial advantage for hyperhidrosis patients in the future. It is well documented that primary hyperhidrosis can be an extremely debilitating condition so clearly a more robust understanding of the condition and effective evaluation of treatment options confers much tangible benefit for patients.

2. **Objectives (include all primary and secondary objectives)**

Primary Objective:

1. To evaluate the effectiveness of the miraDry ® treatment system for psychosocial functioning in patients heavily affected by axillary hyperhidrosis.

Secondary Objectives:

2. To characterize the outcomes of and clinical response to the miraDry ® treatment system with respect to the aforementioned criteria.
3. To compare the results of non-invasive miraDry ® treatment system to the existing surgical correction with respect to the aforementioned criteria.

**3. Background (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)**

Primary hyperhidrosis has been estimated to affect up to three percent of the general population, but remains a disorder of unknown etiology.[1] Excessive sweating due to hyperhidrosis has been shown to have profound effects on patients' physical and mental quality of life, with functional impairments negatively impacting work productivity, daily activities, willingness to participate in social situations, and personal relationships. In particular, patients have been shown to report being extremely limited in developing personal relationships, attending occasions with family or friends, sexual activities, meeting people, public places, and shaking hands.[2]

Primary hyperhidrosis may be often incorrectly assumed to be a symptom of an anxiety disorder, but anxiety is not assumed to be a secondary effect of excessive sweating.[3] Not surprisingly, increased sweating is frequently seen in patients with social anxiety disorder and strongly associated with elevated levels of disability, fear, and avoidance.[4] Studies have shown that hyperhidrosis patients self-report elevated symptoms of psychopathology. However, previous psychological studies have shown that analysis of patients suffering from hyperhidrosis does not yield any evidence of either increased incidence of mental disorders in this group or of a causal role of psychiatric disorders in this condition.[3,5,6] The most recent clinical evidence suggests that the above relationship is consistent with a model of social anxiety simply as a mediator of sweating-related disability, not as a causal factor.[7]

Notably, many patients whose symptoms are refractory to medical therapy may seek endoscopic thoracic sympathectomy which is a surgical correction to cut off the sympathetic outflow to the sweat glands in the palms and axillae.[8,9] Several reports have demonstrated the efficacy of this surgical treatment in patients treated for primary hyperhidrosis, showing significant improvements to physical and mental quality of life[10-12] as well as substantial reduction of anxiety, social phobia, and depression.[6,13,14] These results suggest that a substantial proportion of hyperhidrosis patients with psychological deficits have anxious or depressive characteristics as secondary symptoms of a primarily sweating-related pathology. Although surgical intervention has demonstrated impressive effectiveness in the above regard, it remains an invasive technique with risks associated with all thoracic procedures and the additional risk of focal or generalized compensatory sweating in other areas of the body.[8,9] Therefore, there is an obvious need to explore and develop effective non-invasive treatment systems for primary hyperhidrosis.

MiraDry ® is the trademarked name of a non-invasive thermolytic technology which utilizes a microwave energy-based mechanism targeted for eccrine gland reduction at the dermal-fat interface. The system is designed and marketed by Miramar Labs, Inc. (Sunnyvale, CA) and was FDA cleared for the treatment of axillary hyperhidrosis in 2011. The device itself is a hand-held applicator with a software-driven console device containing the microwave generator calibrated at specified and approved frequencies and power to heat the specified tissue. A multi-center evaluation of the miraDry ® system to treat axillary hyperhidrosis has been conducted and has demonstrated the system's efficacy in reducing severity of idiopathic sweating in the axillae[15] and promisingly suggests the potential for an effective non-invasive treatment option for patients experiencing notable sweating-mediated psychosocial disability and impairment.

## 4. Study Procedures

### a. Study design; including the sequence and timing of study procedures (distinguish research procedures from those that are part of routine care).

This study will seek roughly 24 participants who qualify (for inclusion/exclusion criteria, see Section 5) for a prospective evaluation of the miraDry ® system for psychosocial symptoms related to axillary hyperhidrosis.

Patients will be recruited from both the Johns Hopkins Department of Dermatology and Thoracic Surgery. The recruitment of these patients will occur during normal appointments and clinic visits at Johns Hopkins Hospital. Physicians in either department seeing hyperhidrosis cases will inform patients about the existence of the study. The International Hyperhidrosis Society reserves the right to notify persons regarding the existence of the research being conducted which would amount to no more than a link to the above website. Recruitment will not involve any media advertisements or flyers. The trial will be listed on clinicaltirals.gov and a link will provided to the Hopkins Center for Sweat Disorders website (http://www.hopkinsmedicine.org/sweat_disorders/).

Patients will be asked to complete the Hyperhidrosis Disease Severity Scale (HDSS) as a prescreening survey. The HDSS (below) is a diagnostic tool that qualitatively measures (Likert scaled 1-4) disease-specific severity of the patient's condition based on the degree to which daily activities are impacted:[16]

Hyperhidrosis Disease Severity Scale:
"How would you rate the severity of your hyperhidrosis?"

1. My sweating is never noticeable and never interferes with my daily activities
2. My sweating is tolerable but sometimes interferes with my daily activities
3. My sweating is barely tolerable and frequently interferes with my daily activities
4. My sweating is intolerable and always interferes with my daily activities

A score of 1 or 2 indicates mild or moderate hyperhidrosis while a score of 3 or 4 indicates severe hyperhidrosis. Patients scoring 3 or 4 on the HDSS who also meet the additional inclusion/exclusion criteria will be offered enrollment in the study. The HDSS has been validated for reliability by analysis in three studies and with correlative comparison to the Hyperhidrosis Impact Questionnaire (HHIQ), Dermatology Quality of Life Index (DLQI), and gravimetric sweat production measurements.[16]

These potential participants will be approached directly following their clinical visits. For patients who then agree to participate in the study, written informed consent will be obtained. During the consenting process, the study will be thoroughly explained along with a description of the miraDry ® system and the predicted benefits and possible risks therein. No post-consent screening will be performed. No pre-consent Protected Health Information will be reviewed prior to the signing of consent.

Each participant will schedule an appointment with behavioral medicine and asked to complete additional, survey evaluations (all of which have been independently validated) as listed below. The same slate of surveys will be given at the second appointment and at follow-up.

| Domain | Survey | Applicable Ages |
|---|---|---|
| Dermatology QOL | DLQI | >17 years |
| Broadband psychopathology | BASC | 17-21 years |
| | BASC (college) | 18-25 years |
| Anxiety | Zung Anxiety Self | >17 years |
| Depression | BDI-2 | >17 years |

Each participant will also schedule two miraDry ® treatment appointments approximatelythree months apart. The administration of miraDry ® treatments will take place at Greenspring located at 10755 Falls Road Lutherville, MD 21093.

At each of these treatment appointments, each participant will be asked to complete the above surveys reflecting their current states.

The miraDry ® treatment will be administered using a standard treatment procedure as follows:

- MiraDry system powered on and goes through a self check
- Patient positions self supine on exam table with bilateral axilla exposed by patient placing arms behind head
- Right & left axilla hair bearing area measured and appropriate water tatoo applied to axilla using isopropyl alcohol
- Hibiclens applied to right and left axilla and 1 percent lidocaine with epinephrine 1:100,000 injected at sites indicted by water tattoo
- Sterile KY jelly applied to right and left axilla
- New sterile biotip package opened and connected to MiraDry machine
- Procedure initiated using energy level 3-5, with the number of treatment sites dependent on the size of the hair baring area
- 2 reusable ice packs wrapped in paper towels given to patient to apply to axilla bilaterally

Additionally, study patients will be given the following post-procedure instructions:

- Continue ice packs for the next few days & to always wrap ice pack in a towel to prevent frost bite
- Keep underarms clean using liquid soap to clean the underarms twice a day until the underarm is healed from procedure
- Do not shave underarm until underarm tenderness is resolved and any wounds are healed
- Do not apply antiperspirant or deodorant until underarm tenderness is resoled and any wounds are healed
- Wear loose clothing for 5-7 days to prevent any underarm irritation
- Apply an over the counter antibiotic ointment twice daily to the underarms for 1 week
- An anti-inflammatory over-the-counter drug such as ibuprofen can help manage pain and reduce swelling. It should be taken according to package instructions and as long as there are no contraindications to patient taking this medication.

**b. Study duration and number of study visits required of research participants.**

This study should take approximately 2 years to complete. Participants will be required to be present for at least 4 study visits. The first visit will be for consultation and to determine whether the patient meets the inclusion/exclusion criteria. Then each consented patient will schedule a behavioral medicine appointment for initial psychometric evaluation. This is followed by 2 visits to administer the miraDry ® treatment, spaced approximately 3 months apart. A follow up survey will take place roughly between 6 months and 1 year after the first treatment visit. The follow up visit is optional because the survey will be administered over phone, through the mail, or electronically if the patient is unavailable for study visit.

**c. Blinding, including justification for blinding or not blinding the trial, if applicable.**

This study will compare patient psychometric data at the time of before treatment/consultation to corresponding post-treatment information. Researchers will therefore be blinded to a patient's pre-treatment information when collecting post-treatment data via telephone call or in any situation involving direct patient interaction to eliminate potential bias when soliciting, recording, or analyzing study data.

**d. Justification of why participants will not receive routine care or will have current therapy stopped.**

N/A

**e. Justification for inclusion of a placebo or non-treatment group.**

N/A

**f. Definition of treatment failure or participant removal criteria.**

N/A

**g. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.**

N/A

## 5. Inclusion/Exclusion Criteria

This study will recruit patients diagnosed with focal hyperhidrosis with a known diagnosis of primarily axillary localization. We will only enroll patients available for both treatment visits. Availability for follow-up visit is optional. Only patients between the ages of 18 and 29 years when the first HHIQ is administered will be eligible. The upper age limit was so determined because patients over 29 years often present with psychopathology which is far more recalcitrant to correction of any kind regardless of effectiveness because of the duration of the condition. The lower age limit was so determined because 18 years and up are the ages for which the miraDry ® procedure has been approved for use by the FDA. All participants will be screened using the Hyperhidrosis Disease Severity Scale (HDSS). Only patients reporting their condition as a 3 out of 4 or higher on the HDSS will be eligible for study because preliminary data suggests effective detection of psychological changes only at higher reported levels of sweating severity. A patient's previous non-invasive treatment course, including but not limited to prescription of psychiatric medication and topical therapies, will not justify exclusion from this study.

Patients who are unable to provide informed consent, have known allergies to lidocaine, hibiclens with 4% chlorhexidine, and/or epinephrine, are pregnant (as determined by self-reporting), are unable to take oral antibiotics or antiseptic washes, have heart pacemakers or other electronic device implants, and who need supplemental oxygen are not eligible to participate in this study

## 6. Drugs/ Substances/ Devices

### a. The rationale for choosing the drug and dose or for choosing the device to be used.

MiraDry ® is the only non-invasive thermolytic device approved by the FDA for the treatment of axillary hyperhidrosis. The system's features are described in Section 3. Standard administration of the device will be followed. The device requires the use of a bioTip, which is a sterile, single-patient use consumable that helps ensure safety and efficacy for the patient as well as protection of the equipment.

Lidocaine with epinephrine will be used as a local anesthetic to the treatment site. Additionally, hibliclens with chlorhexidine 4% is an antiseptic antibacterial agent routinely used to prevent the growth of bacteria on the skin and will be used at the treatment site. The drugs used in the study will be the same drug provided for the entire Johns Hopkins Department of Dermatology. There will not be a separate batch of this drug for the sole purposes of this study as this study is not a clinical trial and use of the drug is unlikely to interfere with study results.

### b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.

N/A

### c. Justification and safety information if non-FDA approved drugs without an IND will be administered.

N/A

## 7. Study Statistics

### a. Primary outcome variable.

Pre- and post-treatment scores on the HHDS and other surveys described in Section 4a.

### b. Secondary outcome variables.

Same as primary outcome variable. To compare miraDry ® treatment to surgical intervention, the data collected from the above surveys will be compared to previously collected pre- and post-operative survey data given to surgical patients.

### c. Statistical plan including sample size justification and interim data analysis.

The cohort of axillary hyperhidrosis patients will be constituted by roughly 24 eligible individuals who meet the inclusion/exclusion criteria described in Section 5. This sample size was so determined based on the number of funded complete miraDry ® treatments. However, power analyses of existing clinical data would suggest 80% power to detect statistically significant decreases in anxiety and depressive symptoms with our proposed sample size. Data will be analyzed as it is collected for each study visit stage and again after follow-up for pre- vs. post- treatment comparison.

### d. Early stopping rules.

Each patient has the right to discontinue their participation in the study at any time. All patients who wish to terminate participation in the study will have their request fulfilled effective immediately and indefinitely.

A participant may have their participation in the study discontinued if problems arise during the course of their involvement which require deviations from the approved protocol (section 8c).

## 8. Risks

### a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

Most of these side effects can last from a few days to a few weeks following treatment. Others can last from one to several months or longer as noted.

The most common side effects observed within or near the treatment area follow below.

- Swelling/tightness in the treated area
- Discomfort, tenderness or pain in the underarm when touched, usually treatable with non-prescription medications such as ibuprofen
- Redness from the device suction
- Bruising at the numbing injection sites
- Bumps under the treated area (can last for several months)
- Temporary altered sensation or tingling in small areas of the treated skin or upper arm (can last for several months)
- Partial or total underarm hair loss (can last for several months)

Other less common side effects include:

- Swelling in the adjacent arm or torso (usually lasting a few days)
- Hyperpigmentation (darkening of skin) in the treatment area
- Soreness in the shoulders or arms due to positioning of the arms during the procedure
- Numbness or tingling in the arm due to the anesthesia (usually less than 24 hours)
- Shaking due to epinephrine in the anesthesia (usually lasting less than 24 hours)
- Tight band in the underarm (gradually resolves)
- Small blisters or rashes in the treatment area

There have been rare reports of:

- Altered sweating elsewhere on the body
- Decrease in strength in the arm or fingers that gradually goes away (but can last for several months)
- Pain in the underarm requiring prescription medications
- Infection
- Burns

**b. Steps taken to minimize the risks.**

Risks associated with the system are usually rare or transient. Patients will be made aware of the aforementioned risk factors.

**c. Plan for reporting unanticipated problems or study deviations.**

Any problems involving the medical risk factors listed in section 8a are subject to the early stopping protocol explain in section 7d. Any patient who wishes to discontinue participation will have that request honored immediately and his/her standard treatment will resume unaffected.

The study team will not continue the protocol with a particular patient if a situation arises whereby the study protocol would require modification for continuation with said patient.

Unanticipated problems and potential study deviations will be reported to the JHM IRB.

**d. Legal risks such as the risks that would be associated with breach of confidentiality.**

There exists a minimal risk of a loss of privacy for patients. Information will be collected only by the study PI or designee, and will be stored in password-locked file on a secured computer. Patient confidentially will be protected by not associating any identifying information with the data collected. Collected data will be assigned a numeric code which will be used for data analysis purposes. Survey scripts and any other instances of patient interaction will explicitly state that patient identity and/or patient information will not be linked to responses to questions and surveys.

To ensure the safety and confidentiality of patient and study information, data will be stored on password protected JHH computers and will only be made available to approved study team members.

Medical risk is anticipated to be minimal and unlikely as described in Section 8a. Each enrolled participant will be made aware of the aforementioned risks and will be explicitly made to understand said risks during the consent process.

**e. Financial risks to the participants.**

There is a slight financial risk to the participants in the rare event that the above complications occur requiring additional medical care. Any adverse events, problems and deviations would be reported by the PI directly to the IRB.

**9. Benefits**

**a. Description of the probable benefits for the participant and for society.**

The reported benefits to individual patients with respect to sweating severity are noted above in Section 3 along with our hypothesize benefits with respect to psychosocial functioning.

This research study also potentially offers benefits to all patients who suffer from axillary hyperhidrosis, particularly those experiencing psychological distress or anxiety as a result of sweating. As mentioned in above sections, it is possible that hyperhidrosis patients are at risk of being over-diagnosed with psychotropic medications.

If this study determines that the non-invasive miraDry ® procedure offers relief of secondary psychosocial symptoms of axillary hyperhidrosis, then it offers potential insight and benefits to all primary hyperhidrosis patients for two reasons: (1) those patients can seek more effective medical treatments and (2) those patients will not be exposed to the potential harms involved with psychiatric medications. Additionally, little is known about the pathogenesis and etiology of primary hyperhidrosis so the study of patients with the condition may aid in our study and understanding of the disorder.

**10. Payment and Remuneration**

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

There will not be compensation or payment for participation in this study. Participants will be responsible for payment associated with the behavioral medicine appointment (see Section 11) because that visit is considered standard of care for hyperhidrosis patients. The behavioral appointment is mentioned above and should be considered part of the protocol because baseline data will be collected during the appointment. However, the behavioral medicine appointment is not a unique requirement of this study and is outlined as a standard of care as part of the Johns Hopkins Hospital Center for Sweat Disorders.

**11. Costs**

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

All enrolled participants will have a minimum of one visit with the behavior medicine specialist/psychologist as part of the study. Participants will be responsible for payment

associated with this behavior medicine appointment. With participant consent, information about the appointment will be submitted to a participant's insurance as a health and behavior consultation under their medical diagnosis of hyperhidrosis. As needed, the behavior medicine clinic will obtain necessary pre-authorizations. Participants will be responsible for the portion not covered by their insurance. Depending on the insurance, participants may be responsible for a co-pay, co-insurance, or meeting an existing deductible for the medical coverage. If a participant has not yet met their deductible, then the entire cost of the appointment may be applied toward the deductible, which will depend on the individual insurance plan. During the consent process, participants will receive an explanation of the expected coverage based on their individual insurance plan. Participants will also be advised to inquire with their insurance company for further explanation of benefits and coverage. An exact estimate cannot be provided, as the rates are HSCRC regulated and therefore variable.

This visit will not be billed as a mental health appointment with a psychiatric diagnosis; rather, this visit will be billed as a medical/physical health appointment with a medical diagnosis.

The participant is responsible to pay a total of $1,800 for the 2 miraDry ® treatments. Miramar Labs is supplying 48 biotips for the study at $350 each, totaling $16,800

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