Randomized Pilot Study for the Treatment of Cutaneous Leiomyomas with Botulinum Toxin

Abbreviated Name: Botulinum Toxin for Skin Leiomyomas

Protocol # 09-C-0072

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PRECIS

Background:

- Cutaneous leiomyomas are smooth muscle tumors that may arise sporadically or in association with an inherited cancer-related genodermatosis.
- Leiomyomas may be severely painful, and current management is generally unsatisfactory.
- Studies demonstrate increased nerve density within and around leiomyomas as well as increased acetylcholinesterase staining of associated nerves.
- Botulinum toxin-A has been used in the treatment of pain syndromes.
- Based on the known mechanisms of action of botulinum toxin-A, treatment with botulinum toxin-A (BOTOX®; Allergan, Inc.), may ameliorate the severe paroxysmal pain of symptomatic cutaneous leiomyomas.

Objectives:

- Primary: To assess change in worst lesional pain in the past week based on Brief Pain Inventory (BPI) from Week 0 to Week 4 in treated patients versus controls.
- Primary: To assess improvement in pain based on Visual Analog Scale (VAS) after application of ice at Week 4 compared to baseline in treated patients versus controls.
- Secondary: To assess change in magnitude and in frequency of painful episodes based on a weekly patient diary in treated patients versus controls.
- Secondary: To assess persistence of pain control at Weeks 12 based on the BPI and VAS.
- Secondary: To assess the frequency of rescue pain medication use in treated patients versus controls during the 24 week study period.
- Secondary: To determine the impact of leiomyoma treatment on quality of life.
- Secondary: To assess change in patient's condition based on the Patient Global Impression of Change.
- Secondary: To evaluate the immunohistochemical staining of nerve fibers and muscle in cutaneous leiomyomas in control and treated lesions following the conclusion of the study.

Eligibility:

- Subjects ≥18 years with at least 1 symptomatic cutaneous leiomyoma.
- Pain symptoms must occur at least once a week and be characterized as ≥5 out of 10.

Design:

- A 12-week double-blind placebo controlled pilot study of 18 subjects with symptomatic leiomyomas will include initial assessment with BPI, photography, and skin biopsies, followed by treatment of subjects who initially received placebo.
- Cutaneous leiomyomas will undergo intralesional injection with botulinum toxin-A.
- Subjects will return at Weeks 4 and 12 for repeat assessment using pain and quality of life questionnaires and photography. Skin biopsies will be performed at week 12.

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1 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Study Objectives

- To assess change in worst lesional pain in the past week based on Brief Pain Inventory from Week 0 to Week 4 in treated patients versus controls.
- To assess improvement in patient pain symptoms after application of ice at Week 4 compared to baseline based on Visual Analog Scale in treated patients versus controls.

1.1.2 Secondary Study Objectives

- To assess change in magnitude and in frequency of painful episodes based on a patient diary in treated patients versus controls.
- To assess persistence of pain control at Week 12.
- To assess the frequency of rescue pain medication use in treated patients versus controls during the 24 week study period.
- To determine the impact of leiomyoma treatment on quality of life.
- To assess change in patient's condition based on the Patient Global Impression of Change.
- To evaluate the immunohistochemical staining of nerve fibers and muscle in optional biopsies of cutaneous leiomyomas in control and treated lesions following the conclusion of the study.

1.2 BACKGROUND AND RATIONALE

1.2.1 Leiomyomas

Cutaneous leiomyomas are benign tumors thought to arise from the arrector pili muscle. They may occur as isolated papules, or present as grouped lesions over areas of the body, including the back and extensor surfaces (see Figure 1). Individual lesions often range from 5mm to 1cm in size, but can be as large as a few cm in diameter. Cutaneous leiomyomas have been associated with a dominantly inherited cancer-related genodermatosis, hereditary leiomyomatosis and renal cell cancer (HLRCC), which is caused by a mutation in the fumarate hydratase gene. HLRCC is characterized by cutaneous and (in females) uterine leiomyoma formation as well as an increased risk of renal cell cancer. Patients with HLRCC may present with isolated cutaneous lesions, regional areas of involvement, or diffuse leiomyoma formation.

Both sporadically occurring and HLRCC-related cutaneous leiomyomas are often painful. In some cases, severe paroxysmal pain may be elicited by stimuli as innocuous as pressure or a change in ambient temperature. Cold-induced pain in cutaneous leiomyomas can be reproduced in a standardized setting with application of an ice cube.[1] For patients with symptomatic cutaneous leiomyomas, the pain may be severe enough that patients contemplate suicide.[2] The etiology of the pain symptoms is poorly understood, but the episodic, intense nature of the pain and reported response in some patients to neuroactive agents suggests that manipulation of the nerve conduction pathways may ameliorate pain. The arrector pilorum muscle is under autonomic control. Thus, one would expect that tumors arising from this structure would also be innervated by autonomic nerves that utilize

catecholamine neurotransmitters. Immunohistochemical studies have demonstrated an increase in nerve fibers within and surrounding leiomyomas.[3] Nerves within and around leiomyomas stain strongly with acetylcholinesterase, suggesting a role for acetylcholine in leiomyoma innervation.[4] In murine studies, nerve fibers visualized in the arrector pili muscle are immunoreactive to the neuropeptide calcitonin-gene related peptide (CGRP).[5] The pain is hypothesized to be related to pressure on the nerves within the lesions, release of neuropeptides, or muscle contraction mediated via alpha-adrenergic receptors.[6]

Figure 1. A, Clustering of numerous leiomyomas in a predominantly unilateral distribution on the lower back. B, Solitary leiomyoma on the back of a patient. C, Several discrete leiomyomas scattered on upper midline back and right mid-back ranging in size from 0.5-2 cm. D, Multiple discrete leiomyomas grouped on the right breast.

Treatment of leiomyomas is generally unsatisfactory. In cases of isolated lesions, surgical excision or carbon dioxide laser ablation may be used to remove the lesions. However, surgical and destructive modalities are less attractive options for patients with multiple lesions or patients with involvement of cosmetically sensitive areas. There is also no standard, predictably effective treatment for the pain associated with some of these lesions. Systemic agents which have been using with variable success include phenoxybenzamine, doxazosin, nifedipine, oral nitroglycerin, beta-blockers, and gabapentin. Phenoxybenzamine hydrochloride irreversibly blocks alpha receptors, putatively leading to relaxation of the arrector pili muscle. This drug has several side effects including postural hypotension, reflex tachycardia and gastrointestinal disturbance. Another anti-hypertensive agent, doxazosin, more selectively blocks the alpha-1 receptor, but side-effects include dizziness, headache and

gastrointestinal upset. A treatment that controls the symptoms of severe paroxysmal pain with minimal side effects is needed for cutaneous leiomyomas.

1.2.2 Botulinum toxin-A

Botulinum toxin A (BOTOX®, Allergan), or BTX-A, prevents the presynaptic release of acetylcholine (AcH) at the neuromuscular junction. It is used for the treatment of a number of disorders of the somatic nervous system associated with spasm and dystonia. Increasing experience and appreciation of the safety of the drug, however, has led to expanded use of the agent for a variety of other disorders, including those involving dysfunction of the autonomic nervous system. BTX-A has demonstrated efficacy in smooth muscle disorders of the gastrointestinal tract and bladder tract. Although the mechanism of action of BTX-A in autonomic disorders is less well understood, AcH receptors on autonomic nerve terminals may mediate certain glandular and smooth muscle functions.[7] BTX-A may also exert an effect on sensory transmission of pain via a mechanism(s) independent of acetylcholine blockade. For example, BTX-A has been used in chronic pain syndromes, including musculoskeletal pain, chronic regional pain syndrome, and neuropathic pain.[8 9] Based on *in vitro* and animal studies, proposed mechanisms for the beneficial effect of BTX-A on pain signaling implicate modulation of Substance P, glutamate, calcitonin gene-related peptide, and noradrenaline.[10-13]

Based on long-term high-dose administration of BTX-A in movement disorders, spasticity, gastrointestinal and urological conditions, pain and headache, hyperhidrosis and cosmetic use, local injections of BTX-A are considered to be quite safe.[14] A systematic review of adverse events observed in these patient populations found that only focal muscle weakness and ptosis had a higher incidence in BTX-A-treated subjects versus controls.[15] BTX-A is safely administered in doses of 300 Units or more for disorders such as cervical dystonia.[15 16] The lethal dose, 50% (LD50) dose in rhesus monkeys receiving intravenous BTX-A was 40 U/kg.[17] In humans, BTX-A doses of 20 U/kg have been used safely without systemic toxicity.[18] The maximum allowable dose of BTX-A in this study, 300 U, results in a dose of 4.3 U/kg in a 70 kg adult.

The technique for treating axillary (and palmar) hyperhidrosis utilizes multiple injections of BTX-A spaced 1-1.5cm apart in a grid-like pattern. Given the variability in size, number, and contiguity of symptomatic cutaneous leiomyomas an individual patient may have (see Figure 1), the technique of a BTX-A injection per each 1cm^2 surface area of test site would be comparable.

1.2.3 Rationale

The current treatments for the paroxysmal pain associated with cutaneous leiomyomas are inadequate. Acetylcholinesterase staining is seen in and around leiomyomas,[4] and CGRP immunoreactivity is present in nerve fibers of arrector pili muscles.[5] Based on the reported effects of BTX-A on acetylcholine and CGRP, we

propose that a small number of subjects with symptomatic cutaneous leiomyomas be treated in a pilot study with intralesional administration of BTX-A.

The most likely adverse effect of BTX-A injections to skin tumors would be transient pain during injections.[19-21] The proposed study is a double-blind, randomized placebo-controlled injection of BTX-A versus saline into symptomatic cutaneous leiomyoma lesions/regions, followed by BTX-A injection at week 12 in subjects who initially received placebo at week 0.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

1. Subjects must be age ≥18 years
2. Subjects must have a prior biopsy-proven diagnosis of cutaneous leiomyoma.
3. Subjects must have at least 1 symptomatic leiomyoma or regions ≤ 60 cm^2 of leiomyomas with pain characterized as >4 based on a 10-point scale, indicating pain of at least moderate severity.[22 23]
4. Pain episodes must occur at least once a week.
5. Subjects must have the ability to participate fully and comply with the procedures of the protocol in the opinion of the investigator.
6. Written informed consent has been obtained including consenting to have tissue samples stored, however subjects are allowed to refuse sample storage
7. Negative urine or serum pregnancy test in females of childbearing potential.
8. Subjects who are clinically stable such that they can be expected to complete the 24-week study.

2.1.2 Exclusion Criteria

1. Subjects with allergies to BTX-A.
2. Females with a positive pregnancy test, or who are breast-feeding, planning a pregnancy during the study, who think that they may be pregnant at the start of the study or females of childbearing potential who are unable or unwilling to use a reliable form of contraception during the study.
3. Subjects with neuromuscular junction disorders (i.e. myasthenia gravis or Lambert-Eaton syndrome) or peripheral motor neuropathic diseases (i.e. amyotrophic lateral sclerosis or motor neuropathy).
4. Subjects with infection at the intended sites of injection.
5. Subjects who have had prior Botulinum toxin product within the past 6 months.
6. Subjects with pain resulting from other disease(s), specifically:
    - pain that requires intermittent or ongoing treatment with narcotics
    - severe, debilitating, or acute pain originating from sources other than leiomyomas
7. Subjects taking pain medications, neuroactive agents, or other therapy directed toward treatment of cutaneous leiomyomas concurrently or within 5 days or 5 half-lives (whichever is longer) of BTX-A treatment, other than specified rescue pain medications (see Section 3.6). Patients currently on therapy directed toward OTHER mild to moderate chronic pain will be evaluated on a case-by-case basis for inclusion. Patients with well-controlled mild to moderate chronic pain such as that associated

with osteoarthritis, who do not require narcotic therapy, will NOT be excluded. Aspirin for pain relief or for other indications is also acceptable.

8. Subjects with late-stage cancers or unstable disease (such as hemodynamic instability, i.e., systolic or diastolic blood pressure fall of 20 mm Hg or greater from the stable patient's baseline measurement).
9. A condition or situation that, in the investigator's opinion, may put the subject at significant risk or interfere significantly with the subject's participation in the study.

2.2 SCREENING EVALUATION

Subjects will be recruited from eligible patients currently undergoing evaluation and/or treatment at the NIH Clinical Center. Patient recruitment will also be done through informational recruitment letters to local physicians (Appendix A).

1. Clinical evaluation will be performed by a study investigator who is board-certified in dermatology to confirm presence of symptomatic cutaneous leiomyomas defined as a score >4 on a 10-point pain scale.
2. Confirmation of prior-biopsy-proven diagnosis of cutaneous leiomyomas.
3. In women of child-bearing potential, negative urine or serum pregnancy test within 2 weeks of receiving treatment.
4. Patients who meet all eligibility criteria and have a history of chronic (not acute) pain well-controlled on non-narcotic therapy for causes other than leiomyomas will be evaluated on a case-by-case basis for inclusion. Patients who report or demonstrate clear benefit from their non-narcotic therapy will not be asked to withhold such beneficial therapy during their participation, especially if their therapy does not affect leiomyoma pain and poses no added risk. The source, intensity of the pain, limits to ADLs, treatment modalities, patient risk/benefit and the impact of their therapy on concomitant medications and study outcomes will be evaluated. Patients who take ibuprofen at baseline for other pain indications will be instructed that the combined daily dose of their ibuprofen including "rescue" pain medication may not exceed 3200mg/day; patients who take acetaminophen for other pain indications including "rescue" pain medication may not exceed 4 grams/day, both as outlined in Section 3.6 Concomitant Medications.
   Additionally, the study team will reinforce that patients taking aspirin for cardioprotective prophylaxis or other indications should continue therapy as prescribed, while on study.

2.3 PARTICIPANT REGISTRATION

Subjects seen in the NCI Dermatology Consult clinic will undergo initial screening by the Principal or Associate Investigators. Subjects not seen in the Consult clinic will undergo initial phone screening by the Dermatology Research Nurse or a designated Associate Investigator, followed by a scheduled evaluation at the Dermatology Clinic (301-594-3208). If eligible, informed consent will be obtained.

A registration Eligibility Checklist (http://camp.nci.nih.gov/ccr/welcome.htm) will be completed and faxed to (301-480-0757) the NCI Central Registration Office (CRO) by a member of the research team within 24 hours of the subject signing the consent. After confirmation of eligibility, CRO staff will communicate with the pharmacy to

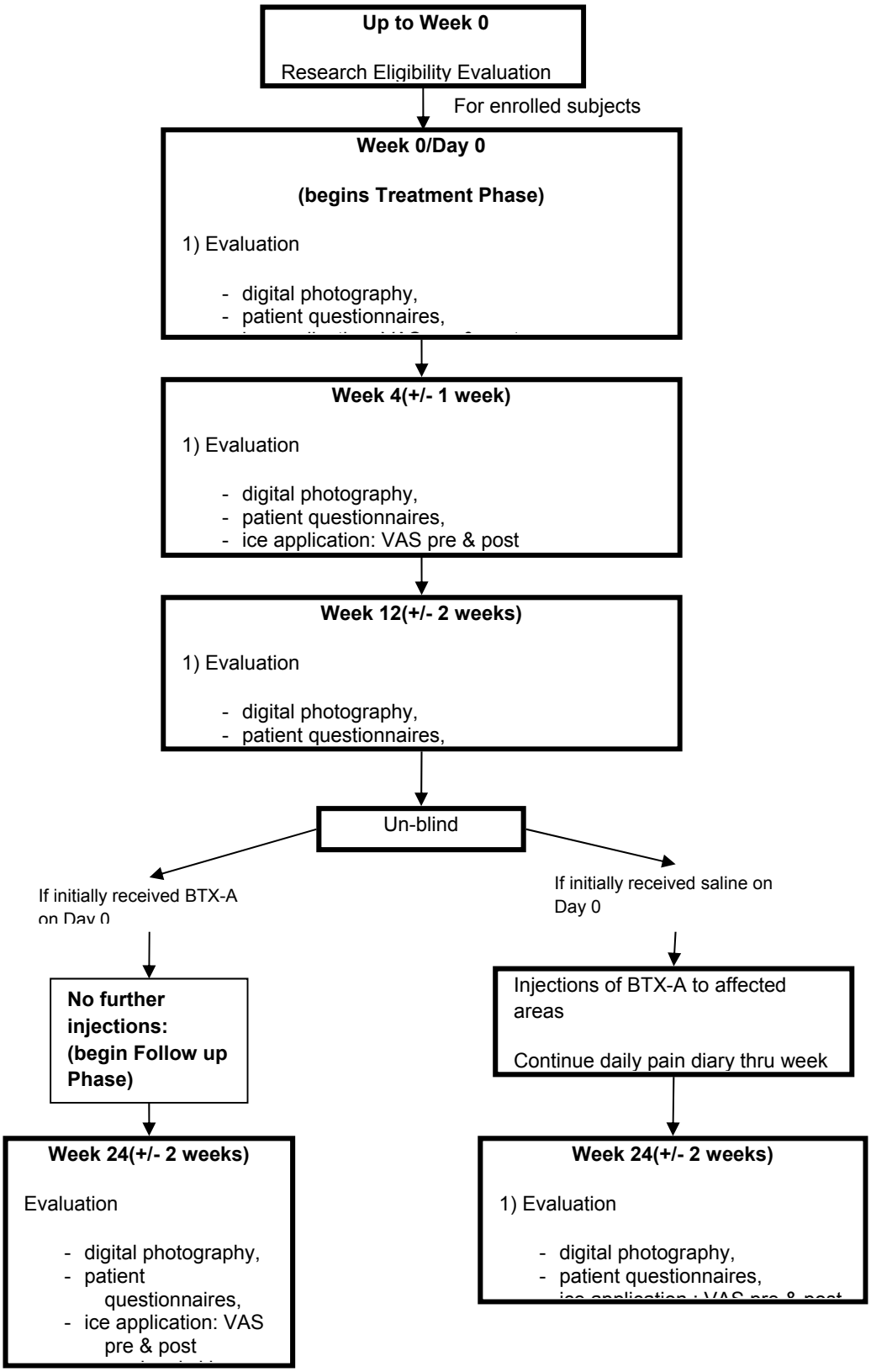
advise them of the acceptance of volunteers on the protocol prior to release of any investigational agents. Verification of registration will be forwarded to the research team electronically via e-mail.

2.4 TREATMENT RANDOMIZATION

At week 0, subjects will be randomized to receive either BTX-A or saline injections. A blocked randomization scheme will be used. After completion of study evaluation at week 12, subjects who received saline injections at week 0 will have the opportunity to receive BTX-A injections.

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN



For this double-blind randomized placebo-controlled study, subjects with symptomatic leiomyomas who meet inclusion criteria will be recruited from subjects seen at the NIH for other protocols or referred from local physicians. Subjects will be recruited through informational recruitment letters to local physicians (see Appendix A) and web page advertisement (www.clinicalstudies.info.nih.gov).

A board-certified dermatologist (Principal or Associate Investigator) will examine study participants to determine study eligibility. If skin lesions are not clinically typical of cutaneous leiomyomas, subjects may undergo skin biopsies to establish histologic diagnosis of cutaneous leiomyomas. Baseline evaluation will include multiple assessment tools such as general pain scales, pain scales prior to/after ice provocation test[1], and quality of life scales (please see Section 3.5 for On-Study Evaluation). After initial assessments are completed, subjects will be randomized to undergo injections of BOTOX® versus saline in cutaneous leiomyomas identified as symptomatic (see Section 3.2 for Drug Administration). Subjects will be allowed use of rescue pain medication during the study period (see Section 3.6 Concurrent medications).

At Weeks 4, 12, and 24, subjects will return to the NCI Dermatology Clinic for follow-up evaluation. Evaluation will include additional assessment tools (see Section 5.2 for On-Study Evaluation). Upon completion of all evaluations at Week 12, the investigator will contact the NIH Clinical Center pharmacist to determine (unblind) if the subject received placebo vs. BTX-A injections. For patients who received BTX-A at Day 0, the follow-up phase begins. For patients who received saline on Day 0, BTX-A injection to the lesions will be offered, thus continuing the Treatment Phase for an additional 12 weeks until their Week 24 evaluation. Maintaining study blinding past Week 12 (i.e. giving saline to subjects who previously received BTX-A) may cause unnecessary pain to these subjects, especially if pain relief was clearly demonstrated. In short, those subjects who initially received placebo will receive BTX-A treatment, but BTX-A treated subjects will not receive saline. After Week 24, if study patients are interested in excision, investigators will confer with them regarding the feasibility of a reasonable cosmetic result following surgical excision. Considering personal/work/travel/other obligations, a period of no more than 1 week before or after the Week 4 visit or 2 weeks before or after the Week 12, or 24 visits may be permitted.

3.2 DRUG ADMINISTRATION

DAY 0: Treatment Phase begins

After test lesions are selected and assessed, the skin surface will be cleansed. The lesions which are most symptomatic will be treated first. Using a 30-gauge needle, injections will have a concentration of 5 Units per 0.1 milliliters of reconstituted BOTOX® versus saline. The concentration of reconstituted BOTOX® to be used for intralesional injection of cutaneous leiomyoma papules/tumors was selected based on the typical dilutions used in dystonias [10 Units per 0.1 milliliters] and in hyperhidrosis [2.5 Units per 0.1 milliliters]. Using a slightly higher concentration than the concentration used in hyperhidrosis will reduce the injection volume in order to minimize subject discomfort.

The actual amount of injected BTX-A will depend upon lesion/region size: A surface area of 1cm^2 will be treated with approximately 5 Units of BTX-A (0.1 ml of fluid). For lesions >1cm^2 or regions with multiple clustered lesions, multiple injections will be performed to maintain the ratio of 5 Units of BTX-A (0.1 ml of fluid) per 1cm^2 of symptomatic lesions. If subjects have an anatomical region with several symptomatic cutaneous leiomyomas, all lesions will be treated up to a maximum of 300 Units of BTX-A, or 60 cm^2 of symptomatic lesions/regions. Placebo saline injections will be administered in the same ratio of 0.1 ml of fluid per 1cm^2 of symptomatic lesions. Although it is safe to administer over 400 Units of BTX-A to patients, subjects will receive up to maximum of 300 Units of BTX-A or the equivalent amount of placebo saline injections.

WEEK 12

Once the study is unblinded, subjects who received saline at Week 0 will be offered BTX-A as outlined above and will continue through the Treatment Phase and completes daily pain self-assessments until Week 24 when final evaluations will be performed.

Subjects who received BTX-A at Week 0 will enter the Follow-up Phase and will not be required to complete the daily pain assessments. These patients will be monitored by phone.

WEEK 24

All subjects will undergo final study evaluations.

3.3 ON STUDY EVALUATION/STUDY CALENDAR

3.3.1 Skin examination, directed history & physical examination

3.3.2 Digital photography of cutaneous leiomyomas with measurement markings

3.3.3 Brief Pain Inventory (BPI)[22] (see Appendix C)

3.3.3.1 (At Week 0) BPI[22] long form, except questions 1-9

3.3.3.2 (At Weeks 4, 12, 24) short form

3.3.4 Dermatology Quality of Life Index (DLQI) (See Appendix D)

3.3.5 10-cm Visual Analog Scale (VAS) before and after ice cube provocation test (apply ice cube wrapped in gauze to entire cutaneous leiomyoma test lesions/regions and controls for 60 seconds[1]) (see Appendix E)

3.3.6 Patient Global Impression of Change (see Appendix F)

3.3.7 Pain Diary Self- Assessment (see Appendix G)

3.3.8 (Optional skin biopsy 12 and 24 weeks after receiving study drug) Skin biopsies of control and injected areas for histologic evaluation. Skin biopsy specimens will be submitted to NCI Pathology and processed for routine histopathology. Subjects with skin lesions in cosmetically sensitive areas may opt to defer skin biopsy. The maximum number of skin biopsies will be 5 (five).

3.3.9 STUDY CALENDAR

	Pre-Treatment	Wk 0	Wk 4 +/- 1 week	Wk 12 +/- 2 weeks	Wk 24 +/- 2 weeks
		Day 0- Day of study drug		Unblind group assignment	
	Eligibility	Treatment Phase: Week 0-12			Weeks 12-24

					BTX-A group: Follow up phase Saline group Continue Treatment Phase
Informed consent	X				
Medical history	X				
Concurrent meds	X	X----------X			
Vital signs	X	X	X	X	X
Skin exam	X	X	X	X	X
Pregnancy test[1,]	X			X[2]	
Adverse event evaluation		X----------X			
Photographs		X	X	X	X
BPI, long form		X			
BPI, short form			X	X	X
DLQI		X	X	X	X
VAS: baseline	X				
VAS: home diary		X----------X			
VAS: Ice cube provocation pre & post measures		X	X	X	X
PGIC			X	X	X
Skin biopsy[3]				X	X

1: In women of childbearing potential

2: In women of childbearing potential who are to receive treatment

3: Optional skin biopsy will be performed 12 & 24 weeks after subjects initially receive study drug and prior to unblinding

All baseline evaluations not completed during the Eligibility period may be completed on Week 0/Day 0 prior to study drug administration.

3.4 CONCURRENT THERAPIES

Rescue pain medication (ibuprofen 400-800 mg every 6 hrs orally as needed for pain, or if contraindicated, acetaminophen 500 -1000 mg every 4-6 hrs orally as needed for pain, not to exceed 4 grams in a 24 hour period) will be allowed during the 24 weeks of the study. Patients will be allowed to continue their prescribed NSAID and reminded to NOT take ibuprofen concomitantly. Patients on chronic ibuprofen therapy for well-controlled chronic pain will be reminded to not to exceed the recommended maximum daily dose of 3200mg/day ibuprofen if rescue pain medication is needed. Patients will be instructed to inform the study team should their prescribed medications for chronic pain be changed or stopped.

Other concurrent treatments directed toward treatment of cutaneous leiomyomas (i.e. pain medications, neuroactive agents, or other therapy taken specifically for cutaneous leiomyoma pain/discomfort) will not be allowed for the 24 weeks of the study.

Concurrent administration of botulinum products for cosmetic or other FDA-approved indications will not be allowed during subject participation in the study.

3.5 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

3.5.1 Criteria for removal from protocol therapy

1. Pregnancy
2. Noncompliance with protocol procedures
3. Observed allergic or non-allergic reactions (in accordance with recent FDA reports as outlined in Section 9.2) to injected study drug

3.5.2 Off Study Criteria

1. Subjects decides to withdraw from the study
2. PI discretion
3. Completion of post-treatment follow-up evaluation
4. Death of patient

NCI CRO must be notified when a patient is taken off study. Off-study forms will be provided or may be obtained from http://camp.nci.nih.gov/dcs/homepgs/offstudy_form.htm.

4 SUPPORTIVE CARE

Communication and consultation with physicians and nurses is available 24 hours a day, 7 days a week through the nursing unit of the NCI Dermatology Clinic or the NIH page operator at (301) 496-1211. When possible, subjects requiring supportive care will be evaluated at the NIH. If a subject is unable to be seen at the NIH, telephone consultation will be available, as described above, to assist other practitioners involved in the subject's

care. Subjects will be screened thoroughly and will be taught to detect early signs of side effects by nurses and physicians.

After administration of BTX-A injections, subjects will be assessed for potential uncommon and temporary side effects such as allergic reaction, fainting, and bleeding. Subjects will be instructed to monitor for other potential rare and temporary adverse effects such as infection.

Punch biopsies are performed under local anesthesia (2% lidocaine with 1:100,000 epinephrine) Non-absorbable sutures will be placed and used for hemostasis. Once hemostasis is achieved, ointment will applied to each biopsy site, and the site will be covered with a sterile dressing. Subjects will be instructed to leave bandages in place for 24 hours. After 24 hours, the biopsy site may be washed with mild soap and water, and new ointment and dressings applied. Sutures will be removed at follow-up evaluation in the NCI Dermatology Clinic.

5 DATA COLLECTION AND EVALUATION

5.1 DATA COLLECTION

Data will be collected on standardized data collection forms during visits (Appendix B) and entered into the database by a data manager assigned to the Dermatology Branch or by a study investigator. Complete unlinked quality assurance records will be maintained on each participant enrolled in the protocol and will be kept by the Principal Investigator. These records will include but are not limited to the following:

1. signed informed consent form
2. written medical history and physical evaluation
3. digital photographic documentation
4. standardized data collection forms (refer to Appendix B)

5.2 RESPONSE CRITERIA

5.2.1 Brief Pain Inventory (BPI) short form & long form[22 23]

The BPI is a validated pain assessment tool that assesses severity of pain, location of pain, impact of pain on daily functions, pain medications, and amount of pain relief in the past 24 hours or past week. The BPI will be administered at Weeks 0 (long form), 4 (short form), 12 (short form) and 24 (short form). (see Appendix C)

5.2.2 Dermatology Life Quality Index (DLQI)[24]

The DLQI is a 10-question quality of life survey which has been extensively validated and frequently used in dermatologic disorders such as atopic dermatitis, acne, and psoriasis. The DLQI will be administered at Weeks 0, 4, 12 and 24 (see Appendix D).

5.2.3 Visual Analog Scale (VAS)

The VAS is a commonly used validated tool for assessment of pain. The 10-cm VAS (see Appendix E) will be used to assess current patient pain/discomfort before and after application of ice to study lesions at 5 time points (eligibility, Weeks 0, 4, 12, and 24). A clinically meaningful change in chronic pain intensity using the VAS has been determined as a reduction of 2 points or 30%.[25]

5.2.4 Patient Global Impression of Change (PGIC)[25]

The PGIC is a validated measure of a subject's assessment of change in pain from baseline. This 7-point categorical scale will be administered at Weeks 4, 12, and 24. (see Appendix F)

5.2.5 Pain Diary Self- Assessment (see Appendix G)

A daily 10-cm VAS will be used by the subject to assess patient pain/discomfort following discharge to home. Patients will also be instructed to list any pain medications taken that day, as well as recording other medications started during their study participation. The forms will be returned to investigators for review at Weeks 4 and 12. If the patient initially receives saline at Week 0 then BTX-A at week 12 (upon un-blinding), he/she will be asked to continue recording the daily pain rating until their Week 24 visit.

5.3 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. The study will utilize the Common Toxicity Criteria CTCAEv3.0 which is available at http://ctep.cancer.gov/reporting/.

Only Grade 3-5 SAEs will be recorded in the C3D database.

5.4 SAMPLE STORAGE, TRACKING, AND DISPOSITION

5.4.1 Future Use of Research Samples

Tissue collected in the course of this research project may be banked and used in the future to investigate new scientific questions related to this study. However, this research will only be done if the risks of the new questions were covered in the consent document. If new risks are associated with the research, the principal investigator will amend the protocol and obtain informed consent from all research subjects.

5.4.2 Storage of tissue

Skin biopsy specimen will be submitted to NCI Pathology for routine histopathology and for immunohistochemistry studies of nerve and muscle tissue. Tissue blocks and slides will be stored per standard NCI Pathology protocol.

A portion of the skin biopsy tissue obtained during study visits may be frozen and stored with the Dermatology Branch, in the Laboratory of Dr Mark Udey. The data recorded for each sample includes the patient ID, name, trial name/protocol number, time drawn, study time point, dose, material type, as well as box and freezer location. All such data will be secured in a locked database/file (to be determined) Samples collected for frozen storage may be sent to the Department of Pathology for immunohistochemical staining.

Samples may also be coded and sent to outside facilities for specialized processing only, after which they will be returned to NIH for analysis. Patient samples sent for outside staining or other processing will be coded (anonymized) via computer-generated code. The PI and designated Associate Investigators will maintain and store the code on a password-protected database.

The PI will report destroyed samples to the IRB if samples become unsalvageable because of environmental factors (ex. broken freezer or shipping problems) or if a patient withdraws consent. Samples will also be reported as lost if they are lost in transit between facilities or misplaced by a researcher. Dr.Udey's laboratory will report any freezer problems, lost samples or other problems associated with samples to the IRB, the NCI Clinical Director, and the office of the CCR, NCI.

Once primary research objectives for the protocol are achieved, intramural researchers can request access to remaining samples providing they have an IRB approved protocol and patient consent.

Samples will be stored permanently unless the patient withdraws consent. If researchers have samples remaining once they have completed all studies associated with the protocol, they must be returned to Dr. Udey's laboratory.

6 STATISTICAL SECTION

The primary objective of this trial is to conduct a small pilot study to determine if there may be an improvement due to use of BTX-A in reported pain attributable to leiomyomas. To ensure that this is not attributable to a placebo effect, the improvement due to use of BTX-A will be compared to that from a placebo-controlled arm.

A total of 18 subjects with symptomatic leiomyomas will be randomized to receive either BTX-A injections or injections of saline, in a double-blind fashion. For patients in both arms, there will be two primary evaluations

performed: one associated with the underlying reported pain from leiomyomas and the other associated with the pain from ice applied to the same site.

The Brief Pain Inventory will be used as the instrument from which the primary endpoint will be obtained; the question, 'On a scale of 0-10, please rate the worst pain you've experienced in the past 24 hours' (the 'main BPI question') will be the primary parameter. This measure will be obtained at baseline. (All other BPI questions will also be asked at each evaluation, but only the one stated above will be considered primary.) Subjects will then be asked to rate their current pain using the VAS. Then ice will be administered for 60 seconds. Subjects will again be asked to rate their current pain using the VAS. Then, BTX-A will be administered, and 4 weeks later the subject will return and be asked the same questions. The change in the main BPI question over 4 weeks will be obtained by subtraction, with the change from baseline to 4 weeks compared between the two groups. Then, ice will be applied again, and the pain intensity question will be asked once again. The difference between the two scores obtained immediately after ice, 4 weeks apart, with and without BTX-A will also be determined by subtraction and the change from baseline to 4 weeks with ice compared between the two groups At 12 weeks, the main BPI question will be asked again, and then following application of ice, the question about pain intensity will be asked once again, resulting in additional paired comparisons of baseline vs. 12 weeks and 4 weeks vs. 12 weeks, both prior to and after receiving ice. Evaluations comparing any of the results obtained at 12 weeks to those at either earlier time point will be considered secondary.

This is intended to be a randomized pilot study which will only obtain preliminary data to determine if the use of BTX-A is able to lessen pain in this setting. With 9 subjects in each arm, there is 78% power to detect a difference in each of the two paired main BPI question scores (from baseline to 4 weeks with or without application of ice) equal to 1 SD of the difference between the two arms, using a one-sided 0.10 alpha level two sample t-test. In practice, a Wilcoxon rank sum test will be used because of the small number of subjects. Since this is a pilot study, no formal adjustment for multiple comparisons will be undertaken, but results will be considered in the context of the two main endpoints being evaluated based on the primary 4 week comparison with baseline.

We will also compare the fractions of subjects with clinical improvement between the two arms. However, since the study will be very small, these differences are not expected to be statistically significant.

If potential benefit is identified in this very small randomized pilot trial, then a larger randomized multi-institutional study will be considered for a subsequent, more definitive evaluation. This study will provide parameter estimates which may be useful in designing this future study.

In addition to the BPI questions, we will request patients to maintain a daily diary of the number and extent of pain episodes over 4 and 12 weeks, and comparisons of these counts and magnitudes of episodes over time will be

performed using appropriate paired comparisons. These diary measurements will also be considered a secondary outcome of the study.

Quality of life measurements based on the Dermatology Life Quality Index will also be obtained in order to determine if there is some evidence of improvements in quality of life by use of this treatment. These measurements will be made at baseline and after 4 and 12 weeks of being on trial.

Optional skin biopsy results obtained 12 weeks after subjects receive BTX-A will be stained for neural markers and these results will be evaluated relative to the impact of BTX-A on pain using non-parametric techniques as appropriate. These evaluations will be considered secondary.

As these are considered to be rarely identified subjects, it is expected that more than 2 years may be required to enroll 18 participants onto this trial.

7 HUMAN SUBJECTS PROTECTIONS

7.1 RATIONALE FOR SUBJECT SELECTION

7.1.1 Selection based on gender, ethnic background or race

Subjects from both genders and all racial/ethnic groups are eligible for this study if they meet the eligibility criteria. To date, there is no information that suggests that differences in disease response would be expected in any one patient group. Efforts will be made to extend accrual to a representative population, but in this pilot study, a balance must be struck between limitations on the number of subjects exposed to a treatment with BTX-A with uncertain benefit on the one hand and the need to explore gender and ethnic aspects of clinical aspects of clinical research on the other. If differences in the outcome are noted to correlate with gender or ethnic identity, accrual may be expanded or a follow-up study may be written to investigate these differences.

7.1.2 Strategies/procedures for recruitment

Referrals from within the NCI and from the community will be welcomed. In addition, a letter describing the protocol will be mailed to potential referring physicians. This protocol also will be available on the internet (www.clinicaltrials.gov).

7.1.3 Justification for exclusions

Subjects that are pregnant or lactating will be excluded from this study. BTX-A is Pregnancy Category C.

7.2 PARTICIPATION OF CHILDREN

Children will not be recruited nor enrolled in this study due to the typical onset of cutaneous leiomyomas occurring after the second and third decade of life and the need for multiple injections.

7.3 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS

7.3.1 Potential benefits to subjects expected from the trial

There is the potential that BTX-A injections may have some benefit in the treatment of leiomyomas based on the current understanding of cutaneous leiomyomas and the mechanism of BTX-A. This research treatment may offer relief of severe pain symptoms. However, benefit cannot be promised, nor can the chance of benefit be accurately predicted at this time. As a result of participating in this trial, subjects will receive evaluation and investigative treatment of their symptomatic cutaneous leiomyomas at the National Cancer Institute's Clinical Center. All the medications, tests, and physician services rendered at the NCI will be free of charge to them.

7.3.2 Alternative approaches or treatments

The risks and benefits of this trial, the treatment requirements, and alternative approaches to entering on this trial will be discussed with subjects prior to enrollment and subjects will be consented verbally and in writing.

7.3.3 Procedures for protecting against or minimizing any potential risks

All care will be taken to minimize side effects, but they can be unpredictable in nature and severity. This study may involve risks to subjects that are currently unforeseeable. Subjects will be examined and evaluated prior to enrollment and at weeks 4 and 12. All evaluations to monitor the treatment of subjects will be performed and recorded in the patient chart. In addition to the Clinical Center health care providers, all subjects will be asked to have a local physician to improve long term care and to monitor for complications. If subjects suffer any physical injury as a result of the participation in this study, immediate medical treatment is available at the NCI's Clinical Center in Bethesda, Maryland. Although no compensation is available, any injury will be evaluated and treated in keeping with the benefits or care to which subjects are entitled under applicable regulations.

7.3.4 Provisions for monitoring data collection to ensure safety of subjects

As information is gathered from this trial, clinical results will be shared with subjects although ensuring total patient confidentiality. Laboratory and clinical data will be gathered and any new significant findings found during the course of the research, which may affect a patient's willingness to participate further, will be explained. Moreover, in all publications and presentations resulting from this trial, subjects' anonymity will be protected to the maximum extent possible; although, authorized personnel from the National Cancer Institute (NCI) may have access to research files in order to verify that patient rights have been safeguarded. In addition, patient names will be given to the NCI CRO, to register and verify patient eligibility.

7.4 RISKS/BENEFITS ANALYSIS

Subjects enrolled on this study will be those who have symptomatic cutaneous leiomyomas with pain level of >4, indicating moderate to severe pain. BTX-A has been used safely for the treatment of movement disorders and pain as well as for cosmetic use. We do not anticipate skin or systemic toxicities with the BTX-A injections to be administered in this research study. Thus, we believe that some subjects participating in this trial may have a positive benefit/risk ratio.

Biopsies collected in the course of this research project may be banked and used in the future to investigate new scientific questions related to this study. However, this research may only be done if the risks of the new questions were covered in the consent document. If new risks are associated with the research the principal investigator must amend the protocol and obtain informed consent from all research subjects.

7.5 CONSENT AND ASSENT PROCESS AND DOCUMENTATION

The investigational nature and objectives of this trial, the procedures and treatments involved and their attendant risks, discomforts, and potential benefits will be carefully explained to the patient or the patient's advocate. This process will include a general description of the disease process, as well as a description of the patient's expected clinical course. Alternative therapies will be fully described, and outlined in the consent document. The patient will be asked to read the consent at his/her convenience and will be encouraged to ask questions. Enrollment on this study will only occur if the patient meets all eligibility criteria, is judged by the Principal Investigator to potentially benefit from the therapy, is able and willing to provide full consent, and has signed the consent document. Moreover, any experimental invasive procedure will require a separate consent form (standard procedure consent form).

8 SAFETY REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

8.1 ADVERSE EVENT DEFINITIONS

8.1.1 Adverse Event

An adverse event is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial associated with the use of a drug in humans, whether or not the event is considered related to the treatment or clinically significant. For this study, AEs will include events reported by the patient, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign or clinically significant laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. All AEs must be recorded on the AE case report form.

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until satisfactory resolution. AEs should be reported up to 30 days following the last dose of study drug. AEs that are considered treatment related, expected, continuing, but not resolvable by 30 days after treatment completion (e.g., alopecia) will not be followed after the 30-day period.

8.1.2 Suspected adverse reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

8.1.3 Unexpected adverse reaction

An adverse event or suspected adverse reaction is considered “unexpected” if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected”, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

8.1.4 Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.1.5 Disability

A substantial disruption of a person’s ability to conduct normal life functions.

8.1.6 Life-threatening adverse drug experience

Any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

8.1.7 Protocol Deviation (NIH Definition)

A protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that is under the investigator’s control and that has not been approved by the IRB.

8.1.8 Protocol Violation (NIH Definition)

Any change, divergence, or departure from the study procedures in an IRB-approved research protocol that has a major impact on the subject's rights, safety, or well-being and/or the completeness, accuracy or reliability of the study data.

8.1.9 Unanticipated Problem

Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to

  (a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and

  (b) the characteristics of the subject population being studied; **AND**

- Is related or possibly related to participation in the research; **AND**
- Places subjects or others at a g*reater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.2 NCI-IRB EXPEDITED REPORTING OF ADVERSE EVENTS, UNANTICIPATED PROBLEMS AND DEATHS

The Protocol PI will report to the NCI-IRB:

- All unexpected serious adverse events that are possibly, probably, or definitely related to the research
- All deaths, except deaths due to progressive disease
- All Protocol Violations or Deviations
- All Unanticipated Problems

Reports must be received by the NCI-IRB within 7 working days via iRIS.

8.3 NCI-IRB REQUIREMENTS FOR PI REPORTING OF ADVERSE EVENTS AT CONTINUING REVIEW

The protocol PI will report to the NCI-IRB:

- All Grade 2 unexpected events that are possibly, probably or definitely related to the research;
- All Grade 3 and 4 events that are possibly, probably or definitely related to the research;
- All Grade 5 events regardless of attribution;
- All Serious Events regardless of attribution.

NOTE: Grade 1 events are not required to be reported.

The following **expected** adverse events will not be reported:

- Associated with BTX-A injections:
  - Transient mild discomfort at test sites

- Fainting
- Bruising

- Associated with skin biopsies:
  - Fainting
  - Mild pain and bruising at the site of biopsy
  - Minor bleeding
  - Mild scarring and/or pigmentary alteration at the site of biopsy

8.4 ALLERGAN EXPEDITED REPORTING OF SERIOUS ADVERSE EVENTS

The protocol PI will report any serious adverse events during the study period immediately, or within 24 hours, to Allergan. Adverse events should also be reported at http://www.fda.gov/medwatch/index.html.

8.4.1 Allergan Assessment of Severity

A clinical determination of intensity of an adverse event. The severity assessment for a clinical adverse event should be completed using the following definitions as guidelines:

- Mild: Awareness of sign or symptom, but easily tolerated
- Moderate: Discomfort enough to cause interference with usual activity
- Severe: Incapacitating with inability to work or do usual activity
- Not applicable: In some cases, an adverse event may be a finding that cannot be graded.

8.4.2 Allergan Assessment of Relationship to Study Drug

A determination of the relationship (if any) between an adverse event and the study drug. The relationship should be determined using the following definitions as guidelines:

- Unrelated: The adverse event is clearly not related to the study drug and is clearly related to an underlying disease, environmental or toxic factors, or other drug or therapy.
- Possible: The adverse event occurred in a reasonable time after study drug administration, but could be related to an underlying disease, environmental or toxic factor, or other drug or therapy. There is a reasonable possibility of a causal relationship between the study drug and the adverse event.
- Probable: The adverse event occurred in a reasonable time after the study drug administration and is likely related to an underlying disease, environmental or toxic factor, or other drug or therapy. The event may respond to stopping the study drug.

- Definite: The adverse event occurred in a reasonable time after study drug administration and is not explained by any environmental or toxic factor, or other drug or therapy. The adverse event should respond to the stopping the study drug and recur on re-challenge (were these to take place).

8.5 Data and Safety Monitoring Plan

The clinical research team will meet on a regular basis when patients are being actively treated on the trial to discuss each patient.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Adverse events will be reported as required above. Any safety concerns, new information that might affect either the ethical and or scientific conduct of the trial, or protocol deviations and violations will be immediately reported to the IRB using iRIS.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

9 PHARMACEUTICAL INFORMATION

9.1 Source

Allergan will supply vials of BTX-A, which will be stored in the CC Pharmacy.

9.2 Reported Adverse Events and Potential Risks

1. Hypersensitivity reactions – Uncommon reports of cutaneous hypersensitivity eruptions (psoriasiform eruption, urticaria, erythema multiforme) have been reported, but the relationship is unknown. Anaphylaxis has been reported in a woman treated with a mixture of lidocaine and botulinum toxin-A for chronic neck and back pain. Subjects will be monitored for 30 minutes after treatment and will be instructed on potential adverse effects of BTX-A injection.
2. Muscle weakness – Weakness can occur as a result of local spread of toxin (see paragraph below). For treatment of hyperhidrosis, injections are intradermal which minimizes BTX-A affecting skeletal muscles.
3. Cardiovascular events – Rare reports of arrhythmia and myocardial infarction have been reported in subjects with risk factors for cardiovascular disease. The relationship between botulinum toxin injection and cardiovascular events has not been established.
4. Local pain and/or bruising – These temporary side effects may occur with BTX-A injection.

5. Teratogenicity – Pregnancy category C. Pregnant subjects are excluded from enrollment in this research study.

While botulinum products offer therapeutic benefits, there have been recent reports and news releases from the FDA announcing serious adverse events. The majority of these adverse events occurred following treatment for muscle spasticity and cervical dystonia. These serious adverse events indicate the effects of the drug may spread from the injection area to other areas of the body. This spread may cause symptoms similar to those of botulism, such as unexpected loss of strength, slurred speech/speech changes, respiratory problems, swallowing difficulty, changes in vision/diplopia or eyelid drooping. Of note, the FDA has not identified any definitive serious adverse event reports of distant spread of toxin effect associated with dermatologic use of botulinum toxin-A.

Enrolled subjects will receive a letter to informing them of this recent FDA news release, advising them to contact us and to seek immediate medical attention if they develop any adverse effects.

Prospective enrollees will be informed during documented face-to-face discussions with reinforcement during the time of consent.

During the blinded study period, we will perform follow-up phone calls and e-mails to all enrolled and future subjects.

9.3 Formulation and Preparation

Each single use vial of BOTOX® contains sterile, vacuum-dried, and preservative-free 100 Units of *Clostridium botulinum* type A neurotoxin complex, 0.5 milligrams of human albumin, and 0.9 milligrams of sodium chloride. Two (2) milliliters of 0.9% sterile, non-preserved saline is used to reconstitute each vial of BOTOX® to yield a concentration of 5 Units per 0.1 milliliter. A new, sterile needle and syringe will be used on each occasion of removing BOTOX® from the vial.

9.4 Stability and Storage

Unopened vials of BOTOX® will be stored in a refrigerator (2-8°C) for up to 24 months. Once opened and reconstituted, BOTOX® will be stored in a refrigerator (2-8°C) and will be administered within 4 hours.

9.5 Administration Procedures

BTX-A will be stored in and distributed by the Clinical Center Pharmacy for use in this research study. The Clinical Center Pharmacy will reconstitute the vials of BOTOX®. The Clinical Center Pharmacy will dispense unmarked vials of saline or reconstituted BOTOX® at a concentration of 5 Units per 0.1 milliliter.

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APPENDIX A - RECRUITMENT LETTER TO LOCAL PHYSICIANS

Dear Colleague:

We are asking you to please refer patients aged 18 years or older who have painful cutaneous leiomyomas. The study will evaluate a treatment for symptomatic cutaneous leiomyomas.

We are seeking subjects

- Who are 18 years of age or older
- With leiomyomas that are symptomatic

Subjects will be evaluated by a dermatologist at the NIH. If enrolled in the study, subjects will receive botulinum toxin-A injections into leiomyomas and will undergo skin biopsies.

We appreciate your time and help. Please contact us with any questions. We look forward to working with you.

Sincerely,

Primary Contacts:

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Dermatology Branch

National Cancer Institute

National Institutes of Health

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APPENDIX B - DATA COLLECTION FORM

Pilot Study for the Treatment of Leiomyomas, 09-C- 0072

Week 0

Date: _____

Patient ID:_____ Age: _____ Sex (circle): M F

Weight _____ kg Height ____cm

T:_____ P:_____/min R:_____/min BP: _____mm/Hg (sitting)

Past Medical History: _____

_____

Current Medications:

Drug/Route	Start date	Stop date	Drug/Route	Start date	Stop date
1. _____			6. _____		
2. _____			7. _____		
3. _____			8. _____		
4. _____			9. _____		
5. _____			10. _____		

Allergies: _____Reaction:_____

Evaluation performed (initial at left once assessment/procedure is performed):

_____Dermatologist assessment/findings:

Lesion#	Anatomical site	Description of Lesion	Size (cmXcm)	Treated?	Units BTX-A
#_____			X_____	□Y/□N	_____
#_____			X_____	□Y/□N	_____
#_____			X_____	□Y/□N	_____
#_____			X_____	□Y/□N	_____

#_____ X □Y/□N

#_____ X □Y/□N

PAIN MEDS/DOSES CURRENTLY PRESCRIBED:

_____

Reason for prescribed pain meds:

_____

□ **Visual Analog Scale (before ice application)**

□ **Brief Pain Inventory (long form)**

□ **Dermatology Quality of Life Index**

□ **Digital Photography**

□ **Visual Analog Scale (after ice application)**

Primary/Associate Investigator signature:_____ Date:_____

Heidi Kong, M.D.

Edward Cowen, M.D.

Pilot Study for the Treatment of Leiomyomas, 09-C-0072

Week 4(+/- 1week)

Date: _____

Patient ID:_____

Weight _____ kg T:_____ P:_____/min R:_____/min BP: _____mm/Hg (sitting)

Interim History: _____

_____

_____

Medications/routes/doses started since last protocol visit:

_____

_____

Evaluation performed (initial at left once assessment/procedure is performed):

_____**Dermatologist assessment/findings:** _____

_____

□_____**Visual Analog Scale (before ice application)**

□_____**Brief Pain Inventory (short form)**

□_____**Dermatology Quality of Life Index**

□_____**Patient Global Impression of Change**

□_____**Digital Photography**

□_____**Visual Analog Scale (after ice application)**

Comments:

Primary/Associate Investigator signature:_____ Date:_____

Heidi Kong, M.D.

Edward Cowen, M.D.

Pilot Study for the Treatment of Leiomyomas, 09-C-0072

Circle one: Week 12(+/- 2 weeks)

or Week 24(+/- 2 weeks)

Date: _____

Patient ID:_____

Weight _____ kg T:_____ P:_____/min R:_____/min BP: _____mm/Hg (sitting)

Interim History: _____

_____

_____

Evaluation performed (initial at left once assessment/procedure is performed):

_____**Dermatologist assessment/findings:**

Lesion#	Anatomical site	Description of Lesion	Size (cmXcm)	Treated?	Units BTX-A
#			X	□Y/□N	
#			X	□Y/□N	
#			X	□Y/□N	
#			X	□Y/□N	
#			X	□Y/□N	
#			X	□Y/□N	

□_____**Visual Analog Scale (before ice application)**

□_____**Brief Pain Inventory (short form)**

☐ _____**Dermatology Quality of Life Index**

☐ _____**Patient Global Impression of Change**

☐ _____**Digital Photography**

☐ _____**Visual Analog Scale (after ice application)**

☐ _____**Optional Skin Biopsy (Location:_____)**

Comments:

Primary/Associate Investigator signature:_____ Date:_____

Heidi Kong, M.D.

Edward Cowen, M.D.

APPENDIX C – BRIEF PAIN INVENTORY (SHORT FORM AND LONG FORM)

STUDY ID# _____ HOSPITAL # _____

DO NOT WRITE ABOVE THIS LINE

Brief Pain Inventory (Short Form)

Date: _____/_____/_____ Time: _____

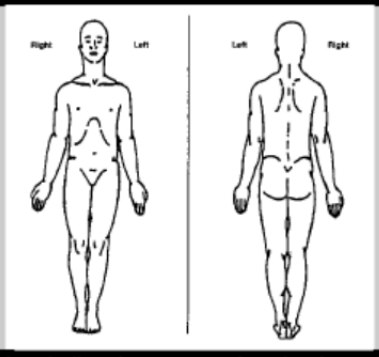
Name: _____ _____ _____

Last First Middle Initial

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

4. Please rate your pain by circling the one nuimber that best describes your pain at its least in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No Relief										Complete Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

C. Walking Ability

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

D. Normal Work (includes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

E. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

F. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

G. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

The Brief Pain Inventory

PROTOCOL # _____ INSTITUTION _____

PATIENT SEQUENCE # _____ HOSPITAL CHART # _____

DO NOT WRITE ABOVE THIS LINE

Brief Pain Inventory

Date: __/__/__

Name: _____ _____ _____

Last First Middle Initial

Phone: (___) _____ **Sex:** ☐ Female ☐ Male

Date of Birth: __/__/__

1) Marital Status (at present)

1. ☐ Single
2. ☐ Married
3. ☐ Widowed
4. ☐ Separated/Divorced

2) Education (Circle only the highest grade or degree completed)

Grade 0 1 2 3 4 5 6 7 8 9

10 11 12 13 14 15 16 M.A./M.S.

Professional degree (please specify) _____

3) Current occupation _____

(specify titles; if you are not working, tell us your previous occupation)

4) Spouse's occupation _____

5) Which of the following best describes your current job status?

1. ☐ Employed outside the home, full-time
2. ☐ Employed outside the home, part-time
3. ☐ Homemaker
4. ☐ Retired
5. ☐ Unemployed
6. ☐ Other

6) How long has it been since you first learned your diagnosis? _____ **months**

7) Have you ever had pain due to your present disease?

1. ☐ Yes 2. ☐ No 3. ☐ Uncertain

8) When you first received your diagnosis, was pain one of your symptoms?

1. ☐ Yes 2. ☐ No 3. ☐ Uncertain

9) Have you had surgery in the past month? 1. ☐ Yes 2. ☐ No

If YES, what kind? _____

10) Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, toothaches). Have you had pain other than these everyday kinds of pain during the last week?

1. ☐ Yes 2. ☐ No

10a) Did you take pain medications in the last 7 days?

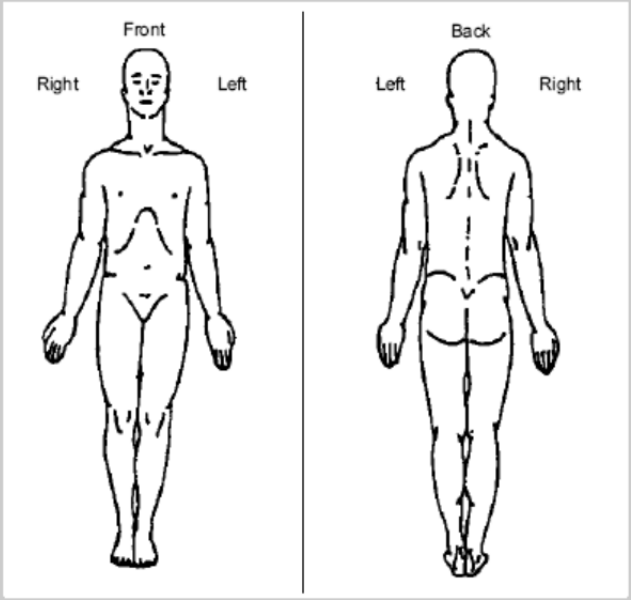
1. ☐ Yes 2. ☐ No

10b) I feel I have some form of pain now that requires medication each and every day.

1. ☐ Yes 2. ☐ No

IF YOUR ANSWERS TO 10, 10a, AND 10b WERE ALL NO, PLEASE STOP HERE AND GO TO THE LAST PAGE OF THE QUESTIONNAIRE AND SIGN WHERE INDICATED ON THE BOTTOM OF THE PAGE.
IF ANY OF YOUR ANSWERS TO 10, 10a, AND 10b WERE YES, PLEASE CONTINUE.

11) On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



12) Please rate your pain by circling the one number that best describes your pain at its worst in the last week.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

13) Please rate your pain by circling the one number that best describes your pain at its least in the last week.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

14) Please rate your pain by circling the one number that best describes your pain on the average.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

15) Please rate your pain by circling the one number that tells how much pain you have right now.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

16) What kinds of things make your pain feel better (for example, heat, medicine, rest)?

_____

_____

17) What kinds of things make your pain worse (for example, walking, standing, lifting)?

_____

_____

18) What treatments or medications are you receiving for pain?

_____

_____

19) In the last week, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No Relief										Complete Relief

20) If you take pain medication, how many hours does it take before the pain returns?

1. ☐ Pain medication doesn't help at all
2. ☐ One hour
3. ☐ Two hours
4. ☐ Three hours
5. ☐ Four hours
6. ☐ Five to twelve hours
7. ☐ More than twelve hours
8. ☐ I do not take pain medication

21) Check the appropriate answer for each item.
I believe my pain is due to:

☐ Yes ☐ No 1. The effects of treatment (for example, medication, surgery, radiation, prosthetic device).
☐ Yes ☐ No 2. My primary disease (meaning the disease currently being treated and evaluated).
☐ Yes ☐ No 3. A medical condition unrelated to my primary disease (for example, arthritis). Please describe condition: _____

22) For each of the following words, check Yes or No if that adjective applies to your pain.

Aching	☐ Yes	☐ No
Throbbing	☐ Yes	☐ No
Shooting	☐ Yes	☐ No
Stabbing	☐ Yes	☐ No
Gnawing	☐ Yes	☐ No
Sharp	☐ Yes	☐ No
Tender	☐ Yes	☐ No
Burning	☐ Yes	☐ No
Exhausting	☐ Yes	☐ No
Tiring	☐ Yes	☐ No
Penetrating	☐ Yes	☐ No
Nagging	☐ Yes	☐ No
Numb	☐ Yes	☐ No
Miserable	☐ Yes	☐ No
Unbearable	☐ Yes	☐ No

23) Circle the one number that describes how, during the past week, pain has interfered with your:

A. General Activity

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

C. Walking Ability

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

D. Normal Work (includes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

E. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

F. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

G. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

24) I prefer to take my pain medicine:

1. ☐ On a regular basis
2. ☐ Only when necessary
3. ☐ Do not take pain medicine

25) I take my pain medicine (in a 24 hour period):

1. ☐ Not every day
2. ☐ 1 to 2 times per day
3. ☐ 3 to 4 times per day
4. ☐ 5 to 6 times per day
5. ☐ More than 6 times per day

26) Do you feel you need a stronger type of pain medication?

1. ☐ Yes
2. ☐ No
3. ☐ Uncertain

27) Do you feel you need to take more of the pain medication than your doctor has prescribed?

1. ☐ Yes
2. ☐ No
3. ☐ Uncertain

28) Are you concerned that you use too much pain medication?

1. ☐ Yes
2. ☐ No
3. ☐ Uncertain

If Yes, why? _____

_____

29) Are you having problems with side effects from your pain medication?

1. ☐ Yes
2. ☐ No

Which side effects? _____

30) Do you feel you need to receive further information about your pain medication?

1. ☐ Yes
2. ☐ No

31) Other methods I use to relieve my pain include: (Please check all that apply)

Warm compresses ☐ Cold compresses ☐ Relaxation techniques ☐

Distraction ☐ Biofeedback ☐ Hypnosis ☐

Other ☐ Please specify _____

32) Medications not prescribed by my doctor that I take for pain are:

_____

_____

Please sign the back of this questionnaire.

Patient's Signature

Thank you for your participation.

APPENDIX D - DERMATOLOGY LIFE QUALITY INDEX (DLQI)

DERMATOLOGY LIFE QUALITY INDEX

DLQI

Hospital No: Date: Score:

Name: Diagnosis:

Address:

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please check one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **yard?**	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
7.	Over the last week, has your skin prevented you from **working** or **studying**?	yes no	☐ ☐	Not relevant ☐
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	☐ ☐ ☐	
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐

Please check you have answered EVERY question. Thank you.

Scoring

The scoring of each question is as follows:

Very much	scored 3
A lot	scored 2
A little	scored 1
Not at all	scored 0
Not relevant	scored 0
Question unanswered	scored 0
Question 7: "prevented work or studying"	scored 3

The DLQI is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired. The DLQI can also be expressed as a percentage of the maximum possible score of 30.

APPENDIX E - VISUAL ANALOG SCALE FOR PAIN

Pilot Study for the Treatment of Leiomyomas, 09-C-0072

Weeks 0, 4, 12, 24

Patient ID:_____

Week __

□ **Pre-Ice Application**

Date: _____ Time: _____ am/pm

Answer the question **"My pain intensity at this time is?"** by marking the line and check the box next to the word that best describes your pain now.

☐ **None**
☐ **Mild**
☐ **Moderate**
☐ **Severe**

No Pain |_____| **Worst Possible Pain**

□ **Post-Ice Application**

Date: _____ Time: _____ am/pm

Answer the question **"My pain intensity at this time is?"** by marking the line and check the box next to the word that best describes your pain now.

☐ **None**
☐ **Mild**
☐ **Moderate**
☐ **Severe**

No Pain —— **Worst Possible Pain**

APPENDIX F - PATIENT GLOBAL IMPRESSION OF CHANGE

Weeks 4, 12, 24

Pilot Study for the Treatment of Leiomyomas, 09-C-0072

Patient ID:_____

Week __

Date: _____ Time: _____ am/pm

Since the start of the study, my overall status is:

1. ☐ **Very Much Improved**
2. ☐ **Much Improved**
3. ☐ **Minimally Improved**
4. ☐ **No Change**
5. ☐ **Minimally Worse**
6. ☐ **Much Worse**
7. ☐ **Very Much Worse**

APPENDIX G - PAIN DIARY

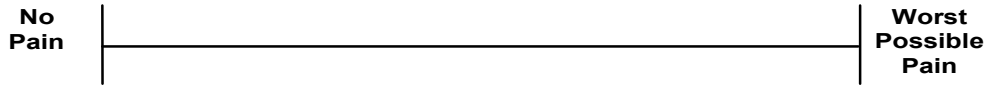
Pain Diary Patient Self-Assessment

**Please complete this form at the same time each day. Please write name & dose of any pain meds taken each day.

Name: _____

Date: _____ Time: _____ am/pm

Answer the question **"My pain intensity at this time is?"** by marking the line.

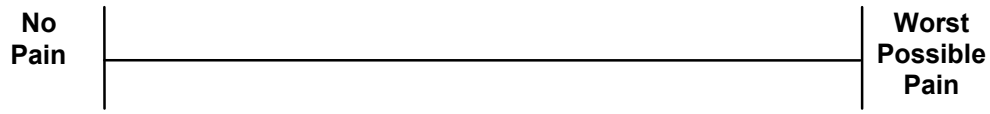


Pain meds used OR new meds started:_____

Initial here _____

Date: _____ Time: _____ am/pm

Answer the question **"My pain intensity at this time is?"** by marking the line.

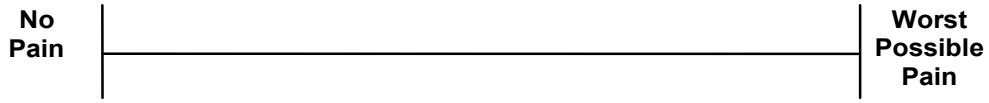


Pain meds used OR new meds started:_____

Initial here _____

Date: _____ Time: _____ am/pm

Answer the question **"My pain intensity at this time is?"** by marking the line.

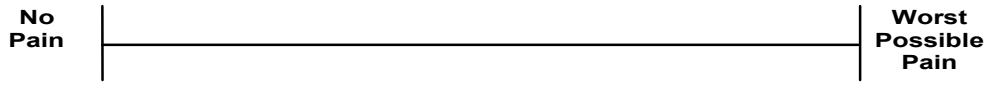


Pain meds used OR new meds started:_____

Initial here

Date: _____ Time: _____ am/pm

Answer the question **"My pain intensity at this time is?"** by marking the line.



Pain meds used OR new meds started:_____

Initial here
