Protocol Title: **The effectiveness of Botulinum toxin on persistent pelvic pain in women with endometriosis**

Abbreviated Title: Botulinum toxin for pelvic pain
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Human Research Protections Program Investigator and Staff Training:

For this protocol, the following "Just in time" human subjects protection training courses are required for investigators and staff:

- CITI GCP modules

Total requested accrual *(separately specify planned accrual for each subject group)*
35 Patients
0 Healthy Volunteers

Project Uses Ionizing Radiation: X No ☐

IND/IDE X Yes *(FDA annual report in PTMS)*
Drug/Device/# Botulinum toxin 113041
Sponsor: National Institute of Neurological Disorders and Stroke

Durable Power of Attorney X No

Multi-institutional Project X No

Data and Safety Monitoring Board X Yes

Technology Transfer Agreement X Yes
Agreement type and number **Clinical Trials Agreement**
Expiration Date_____

Samples are being stored X No

Flesch-Kincaid reading level of consent form: _____
Include reading level for each consent/assent form submitted
(exclude boilerplate in assessing reading level)

PRECIS:

Chronic pelvic pain associated with endometriosis is poorly understood. Some women with chronic pelvic pain have muscle spasm of their pelvic muscles. Muscle spasm may be a significant part of pain in women with endometriosis and other types of chronic pelvic pain. Botulinum toxin injection is widely used to treat conditions associated with excessive muscle activity and spasm. Studies of botulinum toxin injected into pelvic muscles of women with pelvic pain have shown a decrease pain and spasm, but too few women have been studied to conclude its effectiveness. We expect to show that botulinum toxin injection in women with pelvic pain will relieve some of their pelvic pain.

Eligible subjects will be otherwise healthy women who have chronic pelvic pain and a history of endometriosis. Subjects will be randomized to either botulinum toxin injection or placebo (salt water) injection. After one month, we will evaluate the presence of the pain and all women will be offered botulinum toxin injection. We will also evaluate the need for reinjection.

I. Introduction

Chronic pain in women with endometriosis commonly causes them to seek medical care and has a major impact on their quality of life. Chronic pelvic pain has a multifactorial etiology and complex pathophysiology, with an element of spasm of the pelvic floor muscles in many women. Overcontraction of pelvic floor muscles may be a primary source of, or a strong contributor to, the patients' pelvic pain.

Botulinum toxin is an effective treatment for disorders associated with overcontraction of muscles or muscle spasm such as spasticity, dystonia, hemifacial spasm, anismus, and esophageal achalasia. [1, 2] Its use has recently been expanded to treat headache and myofascial pain, where it is believed to act directly on nociceptive pathways as well as on muscle spasm. [3]

There have been several published case reports, uncontrolled clinical trials, and 2 placebo-controlled studies of the treatment of pelvic pain and/or vaginismus with botulinum toxin injection into muscles of the pelvic floor. [4-6] Jarvis et al injected 12 women with chronic pelvic pain, 10 of whom had endometriosis, who had failed more conservative treatment and injection of steroids, anesthetics or phenol. [7] One patient withdrew from the study. The other 11 had significant improvement in pain and on measurement of pelvic floor pressure. Ghazizadeh et al found similar improvement lasting at least 24 months in 24 women. [8] Bartolasi reported complete resolution in vaginismus and reduction in abnormal pelvic floor muscle activity by EMG in 63% of 39 women treated with botulinum toxin A (Dysport®)[9]. Shafik et al compared botulinum toxin (8 women) to placebo injection (5 women) in patients with vaginismus. [10] All of those receiving botulinum toxin improved; there was no improvement in those injected with saline. Abbott et al compared botulinum toxin A to saline placebo in 60 women with vaginismus, chronic pelvic pain and documented elevated intravaginal pressure. They found significant reduction in intravaginal pressure, dyspareunia, and non-menstrual pain along with a trend toward improved quality of life in the botulinum toxin-treated cohort [11].We have treated 3 women with chronic pelvic pain with botulinum toxin as part of standard clinical care. All had decreased pelvic pain lasting up to 9 months. Several case reports have similarly noted relief of pain with injections of botulinum toxin A to pelvic floor muscles in men with chronic prostatic or pelvic pain.[12-14]

Botulinum toxin is the first microbial toxin applicable to the treatment of human disorders. When injected in small amounts intramuscularly, it is rapidly taken up into the presynaptic neuron at the neuromuscular junction where it interferes with acetylcholine exocytosis, irreversibly

blocking neurotransmission at the neuromuscular junction.[3] When used therapeutically for movement disorders, the dose can be titrated to produce sufficient weakness to block the excessive motor activity without paralyzing the muscle. Recovery from injection, due to collateral and axon sprouting with re-establishment of the neuromuscular junction, occurs over approximately 3 months. Thus, most patients require re-injection quarterly in order to maintain benefit, although when used for pain the benefit may be longer.

We have recently observed that women with chronic pelvic pain and any history of endometriosis are significantly more likely to experience central sensitization and myofascial dysfunction than women with chronic pelvic pain without endometriosis or healthy volunteers [15]. Over time, women with endometriosis who have relief from pelvic pain, experience less sensitization and myofascial dysfunction (unpublished data).

While the signs of chronic pelvic pain in women with endometriosis may include pelvic floor spasm, the symptoms women have include pain during menses, intercourse or at other times of the month [16]. Chronic pain has been shown to diminish health-related quality of life (HRQL) using the SF-36 health survey. An endometriosis-specific HRQL questionnaires have been developed [17]. Additionally, individuals with depression or anxiety in addition to their chronic condition such as pain are more likely to report detriments in HRQL [18]. Further, patients with chronic pain commonly experience problems with irritable bowel[19], painful bladder[20] as well as emotional distress, specifically depression, sleep disturbance, and fatigue [21]. In fact, women with endometriosis-associated chronic pelvic pain and myofascial dysfunction often experience diminished quality of life compared to healthy women [22], and may have difficulty having restorative sleep and may be chronically fatigued. Women with chronic pelvic pain associated with endometriosis may experience significant disability as evidenced in the Oswestry Disability index and may experience pain in other body regions which we will capture using the body territories list of the McGill Pain Questionnaire[23].

Assessing the symptoms of pain, endometriosis-related QOL and other measures of quality of life is an important facet of assessing improvement from an intervention such as botulinum toxin. Patient-Reported Outcomes Measurement Information System (PROMIS ®) is an NIH roadmap project establishing self-report measures of health for clinical research and practice [24, 25]. The self-reported measures are drawn from calibrated item banks measuring constructs that are prevalent in chronic illness conditions including Sleep, Fatigue, and Emotional Distress, specifically depression and anxiety. The PROMIS items were administered to a large sample representing the US general population [24] and to multiple groups with chronic diseases [18]. Items are calibrated using a T-score metric with the mean of the US general population equal to 50 and standard deviation [SD] fixed at 10 with higher scores representing more problems with the domain being assessed. Pain catastrophization, a trait associated with depression and anxiety will be assessed as high scores for catastrophization has been associated with less likelihood of improvement from an intervention[26].

Allostasis is the ability to achieve stability, or homeostasis, through change. When presented with stress (or change) over time, a cumulative physiologic effect can be seen, termed allostatic load. McEwen coined this term as a means to quantify “stress-induced damage”, also referred to as “the price the body pays for being forced to adapt to adverse psychosocial or physical situations …”[27]. In this context, allostatic load is directly applicable to the study of pain [28], and can be calculated from measures like blood pressure, body mass index, fasting lipid panel, HbA1C, CRP, morning cortisol and DHEAS.

II. Study objective

To determine the effectiveness of botulinum toxin injection in treating pelvic pain in a cohort with pelvic floor spasm, chronic pelvic pain and a history of surgery for endometriosis.

III. Study Design and Methods

This will be a double-blinded, randomized, placebo-controlled study to determine if botulinum toxin injection can relieve pain associated with pelvic floor spasm in women with chronic pelvic pain. We plan to study women of reproductive age with pelvic muscle spasm and pain persisting after the surgery for endometriosis. Participating women will be randomly assigned to receive either botulinum toxin or placebo (an inactive salt solution) injection. The group of women receiving placebo will serve as controls. Pregnancy tests will be assessed in women who have not had a hysterectomy at the time of botulinum toxin injection and all women will be advised not to become pregnant in the month following injection. Women will be seen again one month after the first injection to assess the effectiveness of injection. Improvement in pain after the first injection will be assessed for the primary outcome. The women will be followed for a year. All participants will be offered a single reinjection with active drug at the one month visit or later during the 1 year follow-up period if the pain returns.

The intent of this protocol is to evaluate whether botulinum toxin injection improves endometriosis-associated pain as reported by the patient and assessed by gynecology and physiatry. Patients will be seen at baseline study injection, one month after the study injection (4-7 weeks), mid-way through the study (5-8 months) and at the end of the study (11-14 months). With regards to Botulinum toxin injections, patients may receive up to 2 botulinum toxin injections (study injection of botulinum toxin or placebo and then 1 additional active botulinum toxin injection– at the one month visit or later during the year after study injection).

IV. Selection of subjects

A. Inclusion Criteria:

- Female gender
- Age between 18 and 55
- History of endometriosis at surgery
- Persistent pelvic pain for at least 3 months
- Pelvic floor spasm
- Negative pregnancy test (in women who have not had a hysterectomy)
- Willing to use reliable method of contraception for the month after botulinum toxin injection including oral contraceptives, IUD, and barrier with spermicide.
- Willing and able to give informed consent
- Willing and able to comply with study requirements

B. Exclusion criteria:

- Women with other causes of chronic pelvic pain including infectious, gastrointestinal, psychological disorders, fibromyalgia and chronic fatigue syndrome based on review of medical history within 1 year of first study visit
- untreated severe cervical dysplasia or other gynecologic condition*
- clinically significant abnormalities on physical or laboratory examinations that require evaluation or treatment or that would make participation unsafe.*
- Hysterectomy and bilateral salpingo-oophorectomy
- Pregnancy
- Lactation
- Allergy to albumen or botulinum toxin
- Presence of antibodies to botulinum toxin or loss of response to previous injections for any indication
- A known neuromuscular junction disorder such as myasthenia gravis or Eaton-Lambert syndrome
- History of urinary or fecal incontinence
- Known pelvic prolapse

**Eligibility will be based on a physical exam at NIH at the first study visit, as well as history and available medical records within 1 year before the study visit. Negative test results will be documented to confirm study eligibility. If the Pap and the GC and chlamydia tests were not done outside of the NIH within the previous year, or if documentation of the negative test results is not available, we will await the results of the screening tests done at the NIH before administering the study medication.*

C. Criteria for withdrawal of subjects from the study

- Inability to perform home monitoring or comply with study visit schedule
- Occurrence of an adverse event that precludes further participation in the study at the discretion of the investigator
- Subject wishes to terminate participation

- Incontinence of urine or feces, or pelvic organ prolapse occurring after injection

D. Study discontinuation

- If more than 2 subjects develop incontinence or pelvic prolapse, the study will be discontinued.

V. Study procedures

A. Screening process: Women with at least a three-month history of pelvic pain suggestive of endometriosis and who have a surgical diagnosis of endometriosis will be considered for this study. Eligible women will complete written consent via telephone interview and will complete a baseline screening questionnaire (appendix 1), one month calendar (appendix 2), and submit records confirming surgical diagnosis.

B. Pre-injection medical evaluation:
This will occur in an outpatient area at the Clinical Center and will include the following for all patients:

1. A complete history including medical conditions, headaches, depression, reproductive health history regarding sexually transmitted diseases, gynecologic conditions, menstrual history, contraceptive use, current hormonal treatment for endometriosis, and pregnancy history.

2. A physical examination including a pelvic exam. The presence of pelvic muscle spasm will be assessed as part of the screening evaluation by study gynecologist.

3. Administration of standardized questionnaires to assess:
    - The presence and severity of dysmenorrhea, deep dyspareunia, and non-menstrual pelvic pain (Standardized Pelvic Pain Questionnaire). A visual analogue assessment will also be performed (Brosens,[16]) (Appendix 3)
    - The quality of life (Endometriosis Health Profile-30) will also be assessed (Jones, [17]) (Appendix 4)
    - Pelvic floor distress inventory (Barber,[29]) (Appendix 5)
    - Patient-Reported Outcomes Measurement Information System (PROMIS ®) measures of health for Anxiety, 7 item measure, Depression, 8 item measure, Fatigue, 4 item measure, Sleep Disturbance, 4 item measure [25](Appendix 6). Patient responses to the questionnaires will not be routinely reviewed during clinic visits. Therefore, we have asked the patient, to communicate directly with the study team if, at any time during her participation, she feels concerned about her mood (anxiety or depression). If a concern is identified in speaking with the patient or reviewing patient responses, the potential for additional services will be discussed.
    - Rome criteria III for Irritable Bowel Syndrome[19](Appendix 14)
    - Painful Bladder Syndrome (Parsons, [20])(Appendix 15)

- SF 36 Health Survey (Appendix 16)
- Oswestry Disability Index (Appendix 17)
- BPI body territories list (Appendix 18)
- Pain Catastrophization Scale (Appendix 19)

4. Laboratory tests: CBC with differential, liver function tests, BUN, creatinine, electrolytes, sed rate, thyroid panel, ANA, Rheumatoid factor, and CPK (15 ml), Pap smear, urinalysis, urine culture, and PCR screening for gonorrhea and Chlamydia at the Clinical Center. The following laboratory tests will occur in the morning with the patient fasting: Fasting lipid panel, fasting glucose, HbA1C, CRP, am cortisol, and DHEAS. The fasting and other blood tests may be drawn on the day of other study procedures or on a separate day, at the participant's convenience.

5. Completing of one month's calendar of medication use and baseline pain score and baseline screening questionnaire (Appendix 1 and 2)

6. Physiatry Assessment for central nervous system sensitization and myofascial dysfunction (Appendix 7)

7. Patient medication guide: patients will receive the botulinum toxin a medication guide for their review (Appendix 8).

C. Injection Procedure

Eligible women agreeing to participate will be randomized to active or placebo injection. The treating gynecologist, the neurologist performing EMG monitoring, and patient will be blinded to the randomization. Injection will be performed during a clinic visit after study eligibility is confirmed. Patients will be instructed not to change any hormonal treatment of endometriosis for the one month following injection.

One hour before injection, up to 10mg of diazepam will be given orally as an anxiolytic and anesthetic cream (lidocaine 4% cream) placed on the vaginal walls. The gynecologist will perform the injection with sterile technique into areas with palpable spasm, under EMG guidance provided by a neurologist. Patients will receive either 100 U type A Botox® (onabotulinum toxin A) reconstituted with preservative–free saline or a similar volume of saline. The location and amount of toxin/saline injected will be documented using a standardized recording sheet (appendix 9). Patients will be able to leave an hour after injection but will be instructed not to drive until the effects of the sedation have worn off.

Randomization will follow a permuted block design with block sizes of 4 and 6. The Pharmacy Development Service, who will not be blinded, will assign the subject. The toxin or saline will be picked up from the pharmacy and prepared by an unblinded nurse in a private, appropriate clinic area. Syringes with the toxin in solution or saline (which are identical in appearance) will be brought to the treatment room.

On the day of botulinum toxin injections, women who have not had a hysterectomy and who are sexually active will have a urine pregnancy test to exclude pregnancy.

D. Post-injection follow-up

Subjects will be asked to complete a one month's calendar of medication use and pain score after injection.

Subjects will be contacted between 3 days and 2 weeks after injection to monitor for adverse effects including genitourinary infections and change in bowel or bladder function.

They will be offered a botulinum toxin injection at 1 month after the first injection, and will return for follow-up clinic visit scheduled at that time. At that visit, the prior month's pain symptoms and use of hormonal treatments and pain medications will be reviewed, and a gynecological examination performed. At the one month visit, several questionnaires will be completed, including: Botulinum toxin patient response inventory (Appendix 10), Standardized Pelvic Pain questionnaire, standardized endometriosis QOL questionnaire, Rome criteria III for Irritable Bowel Syndrome, Painful Bladder Syndrome and PROMIS HRQL measures of sleep, fatigue, anxiety and depression, BPI body territories list, SF 36 Health Survey, Oswestry Disability Score, and pain catastrophization scale. For those opting for a second injection, this will be done as described below.

After the 1-month visit, the patient will be contacted every three months for up to 1 year, to determine how long any effects may have lasted.

E. Second injection

Women who undergo a second injection at the 1 month visit or at any time later within the 1 year follow-up period with the same pretreatment medication, precautions, injection technique, and follow-up as with the first injection. If this injection occurs outside of a scheduled visit, a new baseline will be established to include completion of Standardized Pelvic Pain questionnaire, standardized endometriosis QOL questionnaire, Rome criteria III for Irritable Bowel Syndrome, Painful Bladder Syndrome and PROMIS HRQL measures of sleep, fatigue, anxiety and depression, BPI body territories list, SF 36 Health Survey, Oswestry Disability Score and pain catastrophization scale. All subjects will receive botulinum toxin if a second injection is needed regardless of the randomization group. On the day of botulinum toxin injections, women who have not had a hysterectomy and who are sexually active will have a urine pregnancy test to exclude pregnancy. Women will be asked if they have had urinary or fecal incontinence or pelvic organ prolapse. Those experiencing these symptoms will be systematically assessed and, if significant, will not have an injection. Hormonal treatments and pain medications will be reviewed. One month later, several questionnaires will be completed including: Standardized Pelvic Pain questionnaire, standardized endometriosis QOL questionnaire, Rome criteria III for Irritable Bowel Syndrome, Painful Bladder Syndrome and PROMIS HRQL measures of sleep, fatigue, anxiety and depression BPI body territories list, SF 36 Health Survey, Oswestry Disability Score and pain catastrophization scale. Patients may come for an optional study visit at the one month time point.

Although only the results of the randomized injection will be used for statistical analyses, descriptive data on pain relief will be collected on the outcome of the second injection using the one month calendar of pain and medication use, and botulinum toxin patient response inventory.

F. Mid- and End-Study follow-up

Although only the results of the randomized injection will be used for statistical analyses, descriptive data on pain relief will be collected on the outcome of the additional injection using the one month calendar of pain and medication use, and the botulinum toxin patient response inventory. Additionally, at the mid-way (5-8 months) and study end (11-14 months) study visit,

blood pressure will be checked and a pelvic exam will be done. At the mid-way (5-8 months) and study end (11-14 months) follow-up, the following laboratory tests will occur in the morning with the patient fasting: Fasting lipid panel, fasting glucose, HbA1C, CRP, am cortisol, and DHEAS. The standardized Pelvic Pain Questionnaire and standardized endometriosis-related QOL questionnaire, Rome criteria III for Irritable Bowel Syndrome, Painful Bladder Syndrome and PROMIS HRQL measures of sleep, fatigue, anxiety and depression, BPI body territories list, SF 36 Health Survey, Oswestry Disability Score, and pain catastrophization scale will be assessed. Patient responses to the questionnaires will not be routinely reviewed during clinic visits. Therefore, we have asked the patient, to communicate directly with the study team if, at any time during her participation, she feels concerned about her mood (anxiety or depression). If a concern is identified in speaking with the patient or reviewing patient responses, the potential for additional services will be discussed.

Women who become pregnant after the study injection and one month study visit for the primary outcome assessment and remain in the study (per section B.3 below) may have an additional study assessment beyond the month 12 visit, if needed, to permit a return to baseline status after the immediate post-partum period. The assessment will include completion of study questionnaires and rating scales. An in-person examination and research blood tests (as per the 12 month visit) may also be done, if feasible. These participants may also be offered a 2nd study injection up to one year after delivery or other pregnancy outcome, if they did not have a 2nd injection earlier in the study. Procedures for the later 2nd injection will be per Section E "Second Injection" procedures (above), including data collection, a new baseline assessment, injection procedure and one month assessment.

G. Physiatry assessment for central nervous system sensitization and myofascial dysfunction

At the study end (11-14 months), women will be assessed by the physiatrist for signs of central nervous system sensitization and myofascial dysfunction, and will be assessed by the gynecology team.

H. Medications

Patients may take any medications for pain, to prevent pregnancy, or as treatment for endometriosis. From study initiation to the first month follow-up (4-7 weeks after study injection), subjects will be asked not to initiate or stop hormonal treatment.

Patients should avoid using other drugs that block the neuromuscular junction in the month after injection including aminoglycoside antibiotics and paralytic anesthesia drugs.

I. Data Management

All questionnaires will be administered via a Clinical Trials Survey System (CTSS) of NICHD. The collected self-reported data will be considered the electronic source documentation.
Clinical assessments and other relevant data will be recorded in the Clinical Trials Database.

VI. Botulinum toxin preparation and randomization

The Pharmacy Development Service will use a randomization sequence in blocks of 4 and 6 for this study. When a new patient is scheduled, a member of Dr. Karp's research team will enter the order for coded botulinum toxin/placebo as assigned by the pharmacy. The Pharmacy will dispense the treatment to a research nurse who will prepare the onabotulinumtoxin A -Botox® by reconstitution with saline or saline placebo preparations, arriving in the treatment room with 4 pre-filled one cc syringes on ice. The reconstituted toxin and saline are identical in appearance. Other than the nurse preparing the toxin, neither the patient nor any other member of the research team is aware of treatment assignment.

Onabotulinumtoxin A -Botox® and sterile preservative-free saline are obtained as unopened, intact vials from the NIH pharmacy after it is confirmed that the patient has arrived. The toxin is in the form of a freeze-dried powder that must be mixed into solution. The vial contains 100 units of onabotulinumtoxin A (Botox®). The toxin is prepared in clinic to assure potency, which goes down over time. The solution must be used within 4 hours of preparation.

For this study, the toxin is diluted to a concentration 25 Units/cc by adding 4cc of sterile, preservative-free saline to the 100U Botox® vial using sterile technique. The solution is gently swirled to mix. The diluted toxin is then drawn up into 4- 1cc syringes using sterile technique. The syringes are stored on ice until use. For placebo, 4ccs preservative free saline will be similarly drawn into 4 -1cc syringes using sterile technique and kept on ice until use.

VII. Statistical consideration

A. Outcome measures

Primary Outcome:

1. Improvement in pain – a binary measurement of improvement/no improvement will be used.

Secondary outcome:

1. Need for re-injection at 1 month, as a binary measurement of yes/no
2. Change in Pelvic pain: pain visual analog score
3. Botulinum toxin patient response inventory
4. Standardized Pelvic Pain questionnaire
5. Standardized QOL questionnaire
6. Change in pain medication usage
7. Change in sensitization measures
8. Change in sleep, fatigue, depression or anxiety
9. Rome criteria III for Irritable Bowel Syndrome
10. Painful Bladder Syndrome
11. Change in SF 36 Health Survey
12. Change in Oswestry Disability Score
13. Change in Allostatic load
14. Change in BPI body territories list
15. Association of Pain catastrophization scores with less response to treatment

B. Sample size determination and data analysis

Most women with endometriosis interested in participating in this study of botulinum toxin

versus placebo will be on other treatment (hormones, analgesics, etc). It is unreasonable to expect them to discontinue other treatments for this study, albeit for a short time. A stratified design to account for all different types of potential treatments would be costly and time-consuming and would make it difficult to recruit subjects, especially in the no treatment arm. The randomization itself should take care of all known and unknown confounders. We expect no significant differences in the use of hormones, and other factors between groups. We will not exclude women on hormones.

We will collect information on the use of hormones and all other medications during the study. Furthermore, we will inform patients that they should not initiate or stop hormone therapy from study initiation till the one month follow-up for the primary endpoint. We will monitor women for changes in hormone and other medication use throughout the study.

It is expected that 70% of women receiving active botulinum toxin and 20% of those receiving placebo will report improvement in their pelvic pain at one month. These estimates are from studies of botulinum toxin for back pain and are derived from a report on the effectiveness of botulinum toxin [30]. A sample size of 14 women per group will be required for detecting benefit with 80% power using two-tailed test of significance at $\alpha = 0.05$. We initially allowed for 5% drop-outs/ incomplete follow up. By the time 26 participants had been enrolled, there had been 2 withdrawals from the study. To assure an adequate number of participants completing the full one-year post injection study period, the total accrual ceiling is being raised to 35. Allowing 30 participants to be randomized will provide adequate numbers for analysis should a randomized participant fail to complete the study. Data from all randomized subjects (including withdrawals after randomization) will be included in the analyses.

The primary outcome measure, presence/absence of improvement will be evaluated with Fisher's exact test with somewhat improved and improved a lot considered as improvement, and stayed the same, somewhat worsened and worsened a lot as no improvement.

Secondary outcomes of categorical nature will also be analyzed using Fisher's exact tests. All other continuous variables collected at baseline and follow-up visits, including VAS for pain, improvement and weakness, as well as length of time of benefit, maximal benefit, weakness and maximal weakness, will be compared using t-tests or paired t-tests, as appropriate.

Frequency of side effects and weakness will be tabulated and compared by Fisher's exact test. Hormonal and pain medication variables will be compared between groups and analyses will be adjusted accordingly and as necessary. A $p< 0.05$ will be considered statistically significant. Analysis will be done as intent to treat.

VIII. Event Characterization and Reporting to the IRB, Clinical Director (CD), and Sponsor

Adverse events, protocol deviations, unanticipated problems (UP), Unanticipated Adverse Device Effects (UADEs), serious adverse events, sponsor and serious, are defined as described in NIH HRPP SOP 16 ("Reporting Requirements for Unanticipated Problems, Adverse Events and Protocol Deviations."). All adverse events occurring during the study, including those observed by or reported to the research team, will be recorded in the medical record. Serious unanticipated problems and serious protocol deviations will be reported to the IRB and CD as soon as possible but not more than 7 days after the PI first learns of the event. Not serious unanticipated problems and not serious protocol deviations will be reported to the IRB not more than 14 days after the PI first learns of the event. Serious unanticipated problems will be reported to the DSMB within 7 days. Non-serious and serious deviations that are not unanticipated problems will be reported to

Commented [HR([1]: DSMB Charter says "all unanticipated problems" within 7 days; deviations at the time of yearly meeting. Make consistent.

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the DSMB at the time of its yearly meeting. Serious and non-serious adverse events that occur more than 6 weeks after a study botulinum toxin injection AND are not related to the research will not be reported. All adverse events (regardless of relatedness) within 6 weeks of injection will be tracked and reported as will all adverse events related to the study intervention regardless of time of occurrence.

The PI will immediately report SAEs to the Sponsor according to the requirements of 21 CFR 312.64(b) and as agreed upon with the sponsor. The PI will record nonserious AEs and report them to the Sponsor according to the timetable for reporting specified in the protocol (21 CFR 312.64(b)).

IX. EVALUATION OF RISK AND BENEFITS

A. Evaluation of Benefits:

The study offers the prospect of direct benefit in relieving pain associated with pelvic floor muscle spasm. Although 50% of the patients will initially receive placebo, all women are able to receive active treatment at the time of the one month evaluation.

B. Evaluation of Risks and Discomforts:

The risks and discomforts associated with this study are those associated with the rating instruments, transvaginal injection and with the use of botulinum toxin.

1) Rating scales, interview, Questionnaires:

At the study visits, women will complete questionnaires describing their amount and frequency of pain, side effects, and the effect of the pain on their quality of life. Some subjects may find these types of questions make them feel uncomfortable. Completing these questionnaires will take about 20 minutes of the patient's time. Evaluation of injection outcome using rating scales may be slightly inconvenient, but presents no medical risk.

2) Transvaginal injection

Transvaginal injection can be painful and can cause bruising. Injection discomfort will be minimized by the use of a topical analgesic applied to the vaginal mucosa and an oral anxiolytic. Sterile technique will be used to diminish the remote risk of infection from injection.

3) Botulinum toxin

Botulinum toxin has been used since 1977 and is considered safe by the American Academy of Neurology, and an NIH-sponsored consensus conference [31, 32]. The main adverse effect associated with botulinum toxin injection is more weakness than intended in the injected or adjacent muscles. Such weakness usually improves within 1-2 months of injection. With pelvic muscle injection, the anal or urethral sphincter could possibly be weakened with resultant incontinence. Sphincter weakness is very unlikely with the dose of toxin to be used here and was not seen in the studies cited above, except in a single woman with known prior urinary incontinence. Women with a history of either bowel or bladder incontinence will be excluded

from this study. If incontinence were to occur, it would be transient, resolving over 3 weeks.

A single case report described an ischiorectal fossa abscess following botulinum toxin injection into the obturator internis and pubococcygeus muscles for refractory pelvic pain. The abscess resolved with intravenous antibiotics, incision and drainage. In that case, the injection was done without ultrasound or EMG guidance to assure needle placement in muscle. To avoid infection and abscess in our patients, the vaginal site of injection will be cleaned prior to injection and EMG guidance will be used each tie to assure proper needle placement for intramuscular injection.[33]

Other side effects of botulinum toxin include a flu-like syndrome characterized by myalgias and malaise in the week following injection, especially in patients receiving higher doses than planned here. The symptoms respond well to acetaminophen. There has been a single case report of fatal anaphylaxis in a patient who received botulinum toxin diluted with lidocaine [34]. We will not be preparing the botulinum toxin with lidocaine. Such a severe reaction is highly unlikely.

The FDA requires that all forms of botulinum toxin carry a "black box" warning. In rare cases, botulinum toxin can cause symptoms suggestive of botulism. The symptoms include severe weakness, hoarseness or trouble talking, loss of bladder control, difficulty breathing, trouble swallowing, double vision or blurred vision and drooping eyelids. These symptoms have occurred mainly in children with cerebral palsy who received high doses of botulinum toxin. They can also occur, however, in adults receiving botulinum toxin. Allergan, the company who manufactures the toxin we will be using in this study, has recently developed a patient information pamphlet that we will be handing out to patients as part of the study (Appendix 9).

Offering injection with botulinum toxin at one month is critical to the study design and significantly enhances study enrollment and continuation. The need for the one-month repeat injection is considered a study outcome measure.

There is no safety concern with dose to be used. 100 Units is used at each injection. Those electing the one-month injection, who were randomized to toxin with the first injection, will receive a total of 200 U. The safety of toxin injection with a cumulative dose of 200 U is well established. Many patients receive a dose of 200 U or more at a single injection session. In addition, women with incontinence are excluded from participating.

Neutralizing antibodies to botulinum toxin type A can develop and are more likely in patients receiving high doses or frequent injections. The formation of antibodies is associated with loss of response to further injections with that toxin type. With the one-month interval, at least half of those requesting reinjection will have received placebo. For those receiving toxin with the first injection, the likelihood of antibody formation is exceedingly low as the one-month interval between injections is only used a single time. All other injections are spaced at least 3 months apart.

The risk of botulinum toxin usage during pregnancy is not known. The literature reports several women who received botulinum toxin injections while pregnant without adverse effects on either the mother or fetus. It is not known if toxin injected into a nursing mother could adversely affect the infant. Although women who are pregnant or are nursing are excluded from receiving botulinum toxin in this protocol, we will inform subjects of the unknown risk. Women who become pregnant after the study injection of botulinum toxin or placebo and after the one month study visit needed to assess the primary outcome may continue in the protocol. Pregnant participants may undergo all study outcome assessments but will not be eligible for a 2nd, optional botulinum toxin injection.

The participation of pregnant women in the study under these conditions meets the 45CRF46 subpart B criteria for research with pregnant women as follows:

§46.204 Research involving pregnant women or fetuses.

Pregnant women or fetuses may be involved in research if all of the following conditions are met:

(a) Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;

The research procedures that will be performed in pregnant women include physical examination, phlebotomy with blood volume limited to 10 ml and completion of computer and pen-and-pencil scales and questionnaires. These procedures do not pose risk to pregnant women or fetuses.

(b) The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;

The risks to the fetus from study interventions are not greater than minimal. The purpose of the research is the development of important biomedical knowledge on changes in chronic pelvic pain and response to prior botulinum toxin injection during pregnancy which cannot be obtain by other means.

(c) Any risk is the least possible for achieving the objectives of the research;

The risk is the least possible for achieving study objectives. The risk assessment is minimal risk.

(d) If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, her consent is obtained in accord with the informed consent provisions of subpart A of this part;

Consent of the participant is obtained in accord with 45CFR46 subpart A. The consent form is attached with this amendment request.

(e) If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of subpart A of this part, except that the father's consent need not be obtained if

he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.

Not applicable

(f) Each individual providing consent under paragraph (d) or (e) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;

Full information regarding the reasonable foreseeable impact of the research on the fetus or neonate is provided in the informed consent form

(g) For children as defined in §46.402(a) who are pregnant, assent and permission are obtained in accord with the provisions of subpart D of this part;

Not applicable

(h) No inducements, monetary or otherwise, will be offered to terminate a pregnancy;

No inducements, monetary or otherwise, will be offered to terminate a pregnancy;

(i) Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and

The investigators will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy;

(j) Individuals engaged in the research will have no part in determining the viability of a neonate.

The investigators will have no part in determining the viability of a neonate.

X. Recruitment

Endometriosis is a disease unique to women of reproductive age, therefore only women will be recruited and men and children will be excluded. Every effort will be made to recruit eligible women regardless of their race, as endometriosis occurs in all ethnic groups.

NIH employees are permitted to participate. To avoid any appearance of coercion, there will be no direct solicitation of NIH employees by supervisors. Study staff will assure that the participation or refusal to participate will have no effect, either beneficial or adverse, on the subject's employment or position at the NIH,

The study subjects may be recruited through collaborations with the Uniformed Services University of Health Sciences (USUHS), the Walter Reed National Medical Center (WRNMC), and hospitals served by the NICHD Reproductive Endocrinology Fellowship program. In addition, subjects will be recruited through advertising on the NIH Clinical Center Protocol listings, public service announcements, NIH-approved listservs, websites such as Facebook and Twitter accounts,

ResearchMatch. IRB-approved notices may be sent to physicians treating patients with pelvic pain and endometriosis and women's health and endometriosis support and interest groups for sharing with their members via hard-copy, posting, or distributing electronically.

IRB-approved recruitment notices may be posted on physical and electronic bulletin boards at grocery stores, community centers, bookstores, NIH Clinical Center, libraries or placed in advocacy group offices, in doctor's office waiting rooms, libraries, or retail establishments with approval of the venue and in accord with their policy. Flyers may be made available at outreach exhibits, speaking engagements, support group meetings, parent groups, professional meetings, association/trade meetings with approval of the venue and in accord with their policy. IRB-approved advertisements may be placed in electronic and/or local publications such as newspapers, magazines and support or health care organizations, such as the Washington Post, Express, Gazette, Washington Parent, Washingtonian, Bethesda Magazine, Washington Examiner, Military papers, and Washington Jewish Week, Craig's list and in other paid or unpaid advertising venues.

The IRB-approved advertisements will be used in color as submitted, or may be printed in black and white. The color of the ads may vary. Color changes will not be used to change the emphasis of an ad. The size of the ads may vary, but all parts of the ads, including fonts and pictures, will be changed proportionately to the rest of that ad. Disproportionate changes in size will not be used to change the emphasis of an ad.

All advertisements will be sent to the IRB for review.

Subjects will not be compensated for their participation.

XI. Data and Safety Monitoring

As PI, Dr. Barbara Karp, will serve as the IND Sponsor's medical monitor (SMM). The SMM will make the final determinations of relatedness to the investigational product on behalf of the IND sponsor (NINDS). This study will additionally be monitored by the Data and Safety Monitoring Board (DSMB) per NINDS policy. Additional data and safety and quality assurance monitoring will be performed per NINDS requirements. See section XVIII below for the 12-N-0083 monitoring plan.

XII. Technology Transfer

Botulinum toxin for this study is being provided under a grant and Technology Transfer agreement (Letter of Agreement) from Allergan, Inc (Irvine, CA). Allergan is also providing funds for independent study monitoring.

XIII. Conflict of Interest

The NIH guidelines on conflict of interest have been distributed to all investigators. There are no conflicts-of-interest to report. No NIH investigator involved in this study receives any payment or other benefits from Allergan, Inc.

XIV: Informed Consent

Investigators authorized to obtain consent: The following study investigators are designated as able to obtain consent: Barbara Karp, MD, Pamela Stratton, MD, Codrin Lungu, MD, Melissa

Merideth, MD and Jay Shah, MD.

Consent process: Participants will have the opportunity to carefully review the written consent form and ask questions regarding this study prior to signing. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures and potential risks of the study and of their rights as research participants. The consent form will be signed by the participant, a witness and the investigator obtaining consent. The participant will receive a copy of the consent form for her records. The original signed consent form will be sent to the NIH Medical Records Department.

NIH employees and staff who are interested in participating will be given the "NIH Information Sheet on Employee Research Participation" prior to the consent process. Co-workers from the same Branch or Section will not obtain consent from employees.

XV: Travel and Compensation

Compensation for travel for study visits will be provided within the USA in accordance with NIH policy. Overnight accommodations may be provided if necessary.

Participants (including NIH employees) will not otherwise be compensated for participation.

XVI: Qualifications of Investigators

Barbara I. Karp, M.D., OCD, NINDS is a senior staff neurologist in NINDS with over 20 years' experience in the use of botulinum toxin for neurologic disorders. As the Principal Investigator on this protocol, she is responsible for general oversight and management of the protocol. She conducts study procedures and is authorized to obtain consent.

Pamela Stratton, M.D. is a gynecologist with extensive experience in the management of endometriosis. As the lead AI, she assists with general oversight and management of the protocol, conducts study procedures, and is authorized to obtain consent.

Margaret Bevans, RN, PhD, AOCN, Clinical Nurse Scientist, Dept Nursing, CC. Ms. Bevan provides nursing support for this study. Ms. Bevans does not get informed consent for this study.

Codrin Lungu, MD, Chief, Parkinson's Disease Program, NINDS provides back-up neurological coverage for study procedures, including botulinum toxin injection. Dr. Lungu is authorized to get informed consent.

Melissa Merideth, MD, is a gynecologist with NHGRI who provides back-up gynecological coverage for study procedures, including botulinum toxin injection. Dr. Merideth is authorized to get informed consent.

Jay Shah, MD, Rehabilitation Medicine, CC is a physiatrist and performs physiatry assessments of patients. Dr. Shah is authorized to get informed consent.

Ninet Sinaii, PhD, Clinical Epidemiologist, BCES, OD, CC assists with study design and data analysis. Dr. Sinaii does not get informed consent for this study.

Elaine Considine, RN, HMCS, NINDS is a nurse with experience in botulinum toxin and nursing evaluation of neurologic patients. Ms. Considine is the unblinded investigator who prepares the toxin and placebo for the blinded injections. She does not get informed consent for this study.

NIH trainees, including IRTAs and pre-IRTAs working with study investigators participate in recruitment, screening and assist with data management and scheduling, working under supervision. They do not obtain informed consent.

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XVIII. 12-N-0083 Monitoring Plan

1. Study Staff Responsibilities

Barbara Karp MD, Principal Investigator, is responsible for all aspects of the study. Some responsibilities may be delegated to the current associate investigators: Pamela Stratton MD, Codrin Lungu MD, Melissa Merideth MD, Elaine Considine RN, Margaret Bevans RN, Jay Shah MD, and Ninet Sinaii, PhD.

Delegation of responsibility will be documented on a Signature and Delegation of Responsibility Log.

The NIH Pharmacy will maintain records of randomized study medication dispensed, maintain records of subject identification codes assigned, and have responsibility for releasing randomized codes to investigators at the conclusion of the randomized medication phase. The NIH pharmacy will also have responsibility for the receipt, storage and dispensation of the botulinum toxin and placebo for the study.

2. Source Documentation and Case Report Forms

Dr. Barbara Karp and Dr. Pamela Stratton are responsible for coordinating data collection. One of them will review the data for accuracy and completeness within 48 hours of each subject visit.

The Sponsor, NINDS, has delegated to the PI, Dr. Barbara Karp, the responsibility to conduct and oversee the monitoring for this trial. Patient consent documents, primary outcome and safety laboratory results and diagnostic test results will be monitored for accuracy, correct dating, and agreement between case report forms and source documents. As case report forms are entered electronically into the NICHD Clinical Trials Database, the computer system contains logs indicating changes made and the circumstances leading to these changes.

FDA regulatory requirements (annual reports, adverse events reporting, etc) related to IND #113041 will also be monitored. The medical records of active subjects (defined as subjects receiving study medication) will be monitored on the timetable designated by the monitoring CRO or more frequently as required. The FDA issues will be monitored at least annually. Any major findings will be summarized in writing and reported to the NICHD Institutional Review Board, if indicated. Investigator credentials, training

records, and the delegation of responsibility log will also be reviewed on an annual basis.

3. IRB and DSMB Documentation

All IRB documentation can be found in PTMS. Dr. Barbara Karp is responsible for maintaining IRB correspondence related to this protocol, including records of all reviews of the study and submissions to the IRB.

This protocol meets the requirements for monitoring by a DSMB and will be monitored by the NINDS DSMB. Dr. Barbara Karp is responsible for maintaining DSMB correspondence related to this protocol, including records of all reviews of the study and submissions to the DSMB and the IRB. See the DSMB Charter for details on the Data and Safety Monitoring Plan.

4. FDA Documentation

As the Sponsor, NINDS is responsible for maintaining FDA correspondence, including forms 1571 and 1572 and other correspondence (e.g., annual reports, amendments, and safety reports) in the e-regulatory binder for IND ##113041. Copies of all relevant FDA correspondence are also maintained in PTMS as part of the protocol record.

5. Adverse Event Procedures and Documentation

Adverse events, protocol deviations, unanticipated problems (UP), Unanticipated Adverse Device Effects (UADEs), serious adverse events, sponsor and serious, are defined as described in NIH HRPP SOP 16 ("Reporting Requirements for Unanticipated Problems, Adverse Events and Protocol Deviations). These events will be reported as described in protocol section VIII above.

6. NINDS QA Process

A Contract Research Organization (CRO) will provide on-site monitoring of this protocol. The study team and the CRO monitor will determine the frequency of monitoring visits which will be described in the QA Monitoring Plan. The frequency of visits will include, at a minimum, annual interim monitoring visits until the protocol has undergone a close-out visit, unless otherwise indicated by the Sponsor. The Sponsor via the CRO, will be responsible for providing adequate oversight of the investigation to ensure adequate protection of the rights, welfare, and safety of human subjects and the quality and integrity of the resulting data.

7. Study Completion

Upon completion of the study, Dr. Barbara Karp, Principal Investigator, will retain possession of the IND binder and Protocol Binder in a secure location; for this study, these binders will be maintained electronically in the NICHD CTDB database. FDA requires records be retained for at least 2 years after study completion. HHS regulations require that subjects' records be maintained for at least three years after completion of a study.

Appendices

Appendix 1: Baseline screening questionnaire
Appendix 2: Patient calendar
Appendix 3: Standardized Pelvic Pain Questionnaire (Brosen)
Appendix 4: Standardized QOL Questionnaire (Jones)
Appendix 5: Pelvic floor distress inventory (Barber)
Appendix 6: PROMIS short scales for sleep, fatigue, anxiety and depression
Appendix 7: Physiatry Assessment of Sensitization
Appendix 8: Patient Medication Guide
Appendix 9: Standardized recording sheet for location and amount of toxin injected
Appendix 10: Botulinum toxin patient response inventory
Appendix 11: Deleted
Appendix 12: Data Management
Appendix 13: Consent form
Appendix 14: Rome criteria III for Irritable Bowel Syndrome
Appendix 15: Painful Bladder Syndrome
Appendix 16: SF 36 Health Survey
Appendix 17: Oswestry Disability Index
Appendix 18: BPI body territories list
Appendix 19: Pain catastrophization scale
Appendix 20: Recruitment notices