TITLE:

A Single-Blind, Randomized Study of the BTL Emsella™ Chair versus Sham for the Treatment of Chronic Pelvic Pain

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Study Protocol and Statistical Analysis Plan

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Principal Investigator: Kenneth Peters MD

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STUDY OVERVIEW

Background and Rationale

Chronic pelvic pain (CPP) is a common and often debilitating problem in both men and women. In the literature, the definition is often variable, but a useful clinical definition is pelvic pain that is non-cyclical and of at least 6 months duration [1]. It occurs below the umbilicus and is severe enough to cause functional impairment or require treatment. One of the challenges of treating women with CPP is that a single etiological cause is often lacking. Rather, CPP manifests as a syndrome of symptoms involving gynecologic, gastrointestinal, urologic and musculoskeletal symptoms as well as psychosocial conditions such as depression that negatively impact quality of life

The health care burden of chronic pelvic pain is substantial. However, due to the multitude of possible etiologies, a variety of health care specialists applying different approaches to care, and a lack of a standard definition, the exact prevalence is difficult to determine. CPP is estimated to affect approximately 15% of women with direct cost of physician visits estimated to be over $880 million and the indirect costs due to lost work estimated at $555 million [2]. A more recent study in 2007 projected that between 3.3 and 7.9 million women age 18 years or older in the United States have pelvic pain and other symptoms, such as urinary urgency or frequency, that are consistent with a possible diagnosis of Interstitial Cystitis/Bladder pain syndrome (IC/BPS) [3].

Patients with CPP symptoms often seek care from several different healthcare providers, however even after extensive testing or even surgical treatment they still suffer from chronic pelvic pain. From the clinician's perspective, these patients can be difficult to treat because they do not fit the normal mold of identifiable pathology and predictable response to usual treatments. A definitive diagnosis may be lacking in up to 60% of patients seeking treatment for CPP [4]. One of the problems can be the narrow lens through which health care providers see their patients. A gynecologist may only look for conditions related to the uterus or ovaries or for endometriosis, while urologists may only look in the bladder for pathology, ignoring the surrounding structures. Little is known about how neuronal activity is impacted by CPP. One of the greatest advances in the treatment of CPP is the recognition of the need for multidisciplinary management of these patients [5]. This includes obtaining detailed histories, including assessing for traumatic stress events, co-morbidities, coping mechanisms, attitudes and current health practices. These findings need to be integrated into their plan of care. In addition, treatment outcomes using quantitative, validated tests and questionnaires need to be examined through research. Due to the complex nature of CPP, a synergistic approach may produce greater effect in a shorter period.

Pelvic Floor Dysfunction-Hypertonus (PFD)

Hypertonic pelvic floor dysfunction is often a forgotten and overlooked etiology of CPP. The musculoskeletal system as an unrecognized cause of pain may be an important factor in CPP, specifically the persistent and refractory type [6]. Myofascial pain and hypertonic pelvic floor dysfunction are present in as many as 85% of patients with IC/BPS and/or chronic pain syndromes [7].

The pelvic floor muscles are arranged in deep and superficial layers and act as a sling to support the pelvic organs. The bones and ligaments of the pelvis provide support to the pelvic muscles. The deep levator ani muscles are the most important of the pelvic floor muscles and consist of the pubococcygeus, iliococcygeus, and the coccygeus. They sit deep in the pelvis and are often referred to as the pelvic diaphragm. The levator muscle group was described in detail by Dickenson in 1889. Even then, he recognized the complexity of the muscle group and the role it played in pelvic pathology [8]. The main function of the muscles is in controlling continence and both bowel and urine elimination. The ischiocavernosus, bulbospongiosus, and superficial transverse perineal muscles comprise the superficial layer of the pelvic floor.

The pelvic floor is controlled by both somatic and autonomic motor nerves and neural control is important to understand when evaluating patients for pelvic floor dysfunction [9]. Somatic nerves at S2-S4, referred to as Onuf's nucleus, provide innervation to the anal and urethral sphincter and pelvic floor muscles [10]. The somatic motor fibers leave the spinal cord and form the pudendal nerve which travels through the greater sciatic foramen and heads into the ischiorectal fossa, or Alcock's canal. The pudendal nerve branches into the dorsal nerve of the clitoris, the inferior rectal nerve, and the perineal nerve. These provide sensory innervation to the clitoris, sensory and motor innervation to the anus, and sensory innervation to the labia, distal urethra, bladder, and lower vagina, respectively. The perianal nerve also provides sensory and motor supply to the pelvic floor muscles and external urinary sphincter. The main innervation to the levator ani muscles is from the pudendal nerve and direct S3-S5 branches. Spinal levels L4-S4 provide innervation to the skin of the vulva and the muscles of the pelvic floor [11,12].

The autonomic nervous system along with higher brain centers allows for the precise coordination of events necessary for storage of stool and urine, voiding and defecation, and sexual function. Preganglionic *parasympathetic* nerves are located to the sacral parasympathetic nucleus in the spinal cord at the level of S2–S4. The axons pass through the pelvic nerves and synapse with the postganglionic nerves in either the pelvic plexus, or directly on the end organ. The postganglionic nerves in the pelvic nerve mediate the excitatory input by releasing acetylcholine acting on muscarinic receptors. The *sympathetic* innervation of the pelvic floor originates from the intermediolateral nuclei in the T10- L2 region of the spinal cord. The axons leave the spinal cord via the splanchnic nerves and travel either through the inferior mesenteric ganglia and the hypogastric nerve or pass through the paravertebral chain to the lumbosacral sympathetic chain ganglia and enter the pelvic nerve. The ganglionic sympathetic transmission is mediated by acetylcholine acting on nicotinic receptors.

An important concept to understand when treating pelvic pain is that of cross-system interactions. There is a loss of peripheral specificity when the stimulus arrives in the central nervous system making it difficult to sort out the exact source of the stimulus [13]. In the case of pelvic floor dysfunction, the levator muscles may be stretched and irritated but the patient may perceive it as bladder pain or vaginal pain. This explains why patients with chronic pelvic pain have seen several different specialists because the exact site of pain is difficult to localize.

Patients presenting with pelvic floor dysfunction may have a history of abuse or of intense exercise in which they held their core and pelvic floor muscles tight. They may have a history of being a

competitive dancer, gymnast, diver, cheerleader or horseback rider. Interest in pelvic floor muscle tension as a source of CPP has been evolving over the last 15 years [14]. On physical examination, myofascial trigger points have been described. These hyperirritable bands of muscle can be palpated through the vaginal walls. They are often knot-like or taut and are painful on compression, reproducing the patient's pain symptoms [15, 16] as evidenced by research outcomes of women with CPP who more frequent musculoskeletal findings and less control over their pelvic floor as compared to control subjects [17].

Current Treatments

For those with CPP and urinary symptoms, AUA IC/BPS guidelines include pain management as an essential component to each treatment option [18]. First line treatments involve a multidisciplinary approach and include general relaxation and stress management, patient education, self-care and behavioral modification, and pain management. Second-line agents include physical therapy (avoiding kegel exercises), and oral and intravesical agents. More invasive options include cystoscopy with hydrodistention and neuromodulation as third and fourth-line therapies, respectively.

Pelvic Floor Physical Therapy (PFPT) plays a key role in the evaluation and management of our CPP patients that have been diagnosed with pelvic floor dysfunction. There have been few studies in the literature evaluating the role of manual therapy in CPP patients but those that have been published have been promising [17, 19, 20]. Trigger point injections are another important component of pelvic pain therapy. Several studies have shown the benefit of levator ani trigger point injections [21,22]. If results are good but short-lived with standard trigger point injections, injection of Botox may provide further relief [23,24].

Neuromodulation for treatment of CPP has also been studied. Marcelissen et al performed a review of 10 articles addressing the efficacy of sacral neuromodulation in patients with IC/BPS. The mean reduction in pain scores was between 40% and 72% with follow up between 5 and 87 months. Two articles looked at miscellaneous urogenital pain syndromes with success rates ranging from 60-77% with follow-up between 19 and 36 months [25]. A cohort of 21 refractory IC/BPS patients required 36% less narcotic pain medication after implantation of the Interstim ® device (Medtronic, Inc., MN, USA) [26]. Pudendal neuromodulation has also been studied and has been shown to provide even more benefit than sacral neuromodulation [27].

Emsella Chair

The ideal treatment of CPP is still lacking. Many patients with refractory pain are hesitant to undergo surgical options such as implantation of a sacral neuromodulation device. Current devices require intermittent exchange of the battery and can have issues with MRI compatibility. BTL Emsella™ ("Emsella Chair") may have a role for patients who are not surgical candidates, do not desire surgery, or desire a noninvasive treatment option.

Electromagnetic stimulation of the pelvic floor with the Emsella device is a FDA 510(k) approved therapy whereby a coil generates pulsed electromagnetic fields that penetrate deep into the pelvic floor muscles inducing stimulation and providing rehabilitation of weak pelvic muscles. It was first described as a conservative treatment for stress urinary incontinence (SUI) in 1999 and demonstrated encouraging results [28]. The Emsella Chair is a novel high intensity focused electromagnetic (HIFEM) technology, currently used for the treatment of SUI, in addition to other pelvic floor related disorders. The program phases consist of an intense awakening of the deconditioned pelvic floor muscles (cat), stimulation, and relaxation. The repetition of the phases and focused electromagnetic energy delivery leads to pelvic floor stimulation, adaptation, and remodeling. Alternative settings of pulse strength and frequency could theoretically be used to

stimulate the PFM without inducing muscular contraction. This could induce fatigue in muscle groups, leading to muscle relaxation & reduced hypertonic pelvic floor dysfunction in a manner similar manner to PFPT.

This technology is typically not covered by insurance, is minimally invasive, and safe, but has limited data available. Currently, there is no data available evaluating efficacy of this technology for CPP. The purpose of this study is to compare the Emsella Chair to sham and to determine whether electromagnetic technology is effective in the treatment of CPP.

OBJECTIVES AND ENDPOINTS

Primary Objective - Efficacy

The primary objective of this study is to compare the efficacy of Emsella Chair to sham by evaluating the change in subject-reported pain and discomfort as measured by the Visual Analog Scale (VAS). Mean change in VAS from baseline to end of treatment will be compared between the Emsella Chair group and the sham group.

Hypothesis: Subjects in the Emsella Chair group will show a greater decrease in pain, as measured by VAS, compared to subjects in the sham group.

Secondary Objectives - Efficacy

The secondary efficacy objectives in this study are to compare the Emsella Chair versus sham in relation to several different domains (pain, urinary symptoms, sexual function, quality of life) using validated questionnaires.

- Change in subject-reported impression of CPP severity as measured by the Patient Global Impression of Severity scale (PGI-S)
- Change in subject-reported impression of CPP improvement as measured by the Patient Global Impression of Improvement scale (PGI-I)
- Change in subject-reported pelvic floor tenderness to palpation during 4 quadrant pelvic examination as measured by VAS
- Change in subject-reported sexual function as measured by the Female Sexual Function Index questionnaire (FSFI) for female subjects
- Change in subject-reported sexual function as measured by the Brief Sexual Function Inventory questionnaire (BSFI) for male subjects
- Change in subject-reported depression severity as measured by the Beck Depression Inventory (BDI)
- Change in subject-reported bother related to overactive bladder symptoms as measured by the Overactive Bladder Questionnaire-Short Form (OAB-Q)
- Change in subject-reported urinary and pain symptoms, as well as bother, as measured by the Interstitial Cystitis Symptom Index and Problem Index (ICSI-PI)

- Change in subject-reported anxiety symptoms as measured by the Generalized Anxiety Disorder Questionnaire (GAD-7)

- Change in subject-reported pain as measured by the McGill Pain Questionnaire (MPQ)

- Change in subject-reported rumination, magnification, and helplessness related to pain as measured by the Pain Catastrophizing Scale (PCS)

- Patient-Reported perception of overall improvement in symptoms as measured by Global Response Assessments (GRA) for Pain and Quality of Life

Secondary Objective – Durability
The secondary durability objective for this study is to determine whether subjects in the Emsella Chair group continue to have decrease in pain, as measured by VAS, compared to the Sham group 4 weeks after the primary efficacy endpoint.

Secondary Objective - Safety
The secondary safety objectives of this study are to determine the safety and tolerability of Emsella Chair compared to sham. Safety and tolerability will be assessed in relation to the following:

- Incidence of adverse events (AEs)

Exploratory Objective
- None

Endpoints
The primary efficacy endpoint is 4 weeks after completing all treatments; week 8 of the study. Treatment durability will be assessed 4 weeks after the primary endpoint; week 12 of the study.

Safety Assessment
Adverse events will be assessed beginning at study enrollment (date of randomization) through the completion of the durability or follow up period. The investigator is responsible for reporting all AEs that are observed or reported during the study regardless of their possible relationship to study treatment or their clinical significance.

Safety will be monitored via subject-reported health status and AE reporting at every visit throughout the study period.

METHODOLOGY
This is a prospective sham-controlled observational study of subjects undergoing electromagnetic perineal stimulation for the treatment of CPP. Approximately 60 women and men will be enrolled in this study. Most subjects are expected to be recruited from the Women's Urology and Pelvic Health Center and private Urology offices. Informed consent will be obtained before any study activities are conducted. Subjects who meet all the eligibility criteria will be enrolled in the study and randomized (1:1) to receive Emsella Chair or sham treatments. The subject and biostatistician will be blinded to the group allocation throughout the study. Initial analysis of the data, performed by the biostatistician, will not include group

assignment. Eight treatments (two treatments per week for 4 weeks) with the Emsella Chair to the pelvic floor muscles will be performed.

All study activities, including treatments, will take place in the Urology Research office located on Beaumont's Royal Oak campus in the Medical Office Building, Suite 432. Treatments will be delivered by delegated Urology Research staff, who are key study personnel. Ideally, subjects will receive two treatments per week with sessions separated by at least 2 days. Since the Emsella Chair is non-invasive, the subject remains fully clothed for treatment delivery. The subject will experience tingling and pelvic floor muscles' contractions during the treatment. The subject may resume daily activities immediately after the treatment.

For treatment delivery, subjects will be asked to sit on the device and the height will be adjusted until the subject's feet are on the floor. The active treatments are individualized, since some subjects will be more sensitive than others, and thresholds may vary from visit to visit. The Emsella Chair will be turned on and the setting gradually increased to the subject's sensory threshold; the maximum sensation the subject can tolerate, with the goal of a minimum 50% setting. The subject will not be left unattended throughout the treatment session. The treatment threshold should be increased with every treatment until the subject reaches 100%.

Sham subjects will be positioned on the device in the same manner. The sham treatment will provide some sensation without active HIFEM technology. The programming for the sham treatment will have an amplitude limitation, with the setting below therapeutic level (<10% power).

Regardless of group assignment, each treatment is ≤ approximately 28 minutes at which time the device automatically shuts off. If at any time point, there are two treatment visits where the subject cannot tolerate a setting of at least 50%, they will be withdrawn from the study at the second occurrence. If a subject cannot endure the entire treatment duration, they will be withdrawn from the study.

The primary endpoint for follow up evaluation will be 4 weeks after completion of the last treatment (week 8 of the study). The durability endpoint is 4 weeks following the primary endpoint (week 12 of the study).

At each clinic visit, study procedures will be performed as specified in the table of events, located in Appendix A.

Study subjects will not be compensated for their participation in the trial. However, all research related activities, specified on the table of events, will be provided at no cost to the study subject.

TREATMENT ALGORITHM

Emsella Chair (2 times/week for 4 weeks)	Sham Emsella (2 times/week for 4 weeks)

Treatment Group Assignment

Subjects meeting all eligibility criteria will be randomized to the active treatment group or sham in a 1:1 ratio.

RANDOMIZATION and BLINDING

The study will be performed in a single-blind manner (subject and biostatistician will be blinded to treatment). Subjects will be randomized 1:1 to active Emsella Chair treatment or sham treatment. Subjects will be enrolled in the study and randomized:

- After all screening activities have occurred and it has been determined that the subject meets all inclusion criteria without the presence of exclusionary criteria.
- After the subject agrees to enroll and comply with the study protocol, regardless of study group assignment.

The process of randomization will be as follows:

- Randomization will be performed using a computer-based random number generator. Randomization envelopes will be provided by the study's biostatistician and will be securely stored in a locked cabinet.
- Delegated study staff will solely be responsible for opening the randomization envelopes and delivering the study treatments, according to the group assignment. Ultimately, they will be responsible for maintaining the confidentiality and security of the randomization envelopes and the Subject and Enrollment and Randomization Log.
- After the participant is randomized, the delegated study staff will complete the *Subject Enrollment and Randomization Log.* The study the log will be stored in the regulatory binder.
- The biostatistician will prepare more envelopes, if necessary.

Breaking the Blind

A subject's treatment assignment will not be broken until the end of the study unless medical treatment of the subject is dependent on knowing the study treatment the subject received. If the blind needs to be broken because of a medical emergency, the investigator may unblind an individual subject's treatment allocation.

STUDY ASSESSMENTS AND PROCEDURES

Screening: Visit 0

Before performing any research activities, the study will be explained in detail and adequate time will be allowed for answering questions. If the subject decides to pursue study participation, they will sign the institutional review board (IRB)-approved informed consent document.

Once informed consent is obtained, a study identification number will be assigned. A detailed interview will be conducted, including demographics, medical history, past surgical, gynecological and obstetric history (if applicable), and concomitant medications. Subjects will complete a baseline visual analog pain scale. Weight will be measured. Females will undergo a gynecologic pelvic examination, which includes assessment of levator muscle tenderness. For male subjects, a digital rectal examination will be performed to assess levator muscle tenderness. A dipstick urinalysis will be performed. If positive for leukocytes, a urine culture will be sent. If a subject has a confirmed symptomatic urinary tract infection

(UTI) per investigator's clinical judgment, they will be deferred from screening until treatment is completed and may resume once symptoms resolve. If the female subject is of child-bearing potential, a urine pregnancy test will be performed. If the urine pregnancy test is positive, the subject will be ineligible for study participation. Subjects will complete self-administered questionnaires (PGI-S, FSFI or BSF, BDI, OAB-q, ICSI-PI, GAD 7, MPQ, PCS). Adverse events will be assessed at each study visit including the screening visit. Screening activities may be completed at Visit 1, prior to randomization, if needed. Data collected prior to randomization will be considered baseline.

Study Visit 1: Week 1
A urine pregnancy test (if applicable) will be performed. If the urine pregnancy test is positive, the subject will be ineligible for study participation. Additionally, any screening activities that were not completed at the initial visit will be conducted. After all screening activities are completed, and it is determined that the subject meets the eligibility criteria, the subject will be enrolled in the study and randomized to one of the two intervention arms. The first treatment will be conducted at this visit.

The subject will complete VAS before and after treatment. Concomitant medications and adverse events will be reviewed and changes from the previous visit will be recorded.

If at any time a patient reports a fever, an oral temperature will be obtained. If a fever, defined as $\geq$ 38° Celsius, is present, treatment will be delayed until the fever is resolved at a later visit.

Study Treatments: Visit 2-Visit 8
Subjects will return 2 times per week for Emsella Chair or sham treatments for 4 consecutive weeks. Treatments will ideally be delivered at least 2 days apart from one another. Should scheduling challenges occur, the goal will be to complete all 8 treatment visits within a 6-week window. Prior to conducting the first treatment each week a urine pregnancy test (if applicable) will be performed. If the urine pregnancy test is positive, the subject will be withdrawn from the study. VAS-pain will be completed by subject pre- and post each treatment visit. Additionally, before each second weekly treatment visit, the subject will complete the PGI-I and PGI-S. At visit 8, the subject will complete a treatment blinding assessment, indicating if they believe they received active of sham treatment. Concomitant medications and adverse events will be reviewed and changes from the previous visit will be recorded.

If at any time a patient reports a fever, an oral temperature will be obtained. If a fever, defined as $\geq$ 38° Celsius, is present, treatment will be delayed until the fever is resolved at a later visit.

Urine dipstick will not routinely be collected for analysis at the study treatment visits. However, as standard of care, if UTI symptoms are reported by the subject, urinalysis via dipstick will be performed. If positive for leukocytes, a urine culture will be sent, and the subject will be treated appropriately. Subjects will be allowed to continue study treatments if they are being treated for a UTI, unless they have a fever, defined as temperature ≥ 38° Celsius.

Follow-up Visits
Visit 9, Week 8, Primary Endpoint

Approximately 4 weeks after finishing treatment, the subject will return to the study site for a clinic visit. A dipstick urinalysis will be performed. If positive for leukocytes, a urine culture will be sent. If the subject has a confirmed symptomatic UTI, per investigator's clinical judgment, the remaining activities for this visit will be postponed until treatment is completed and symptoms have resolved. The subject will complete the VAS, PGI-I, PGI-S, FSFI (females only) or BSFI (males only), BDI, OAB-q, ICSI-PI, GAD7, MPQ, PCS, and GRA. Concomitant medications and adverse events will be reviewed and changes from the previous visit will be recorded. For female subjects, a gynecologic (female) or digital rectal (male) exam will be completed with palpation of levator muscles for assessment of tenderness.

Visit 10, Week 12, Secondary Endpoint
Approximately 8 weeks after finishing treatment, the subject will return to the study site for a clinic visit. The subject will complete the VAS, PGI-I, PGI-S, FSFI (females only) or BSFI (males only), BDI, OAB-q, ICSI-PI, GAD7, MPQ, PCS, and GRA. Concomitant medications and adverse events will be reviewed and changes from the previous visit will be recorded.

After completing all visit activities, the subject will be unblinded to treatment group. If subjects were in the sham group, they will be offered the opportunity to receive Emsella Chair treatments. Subjects choosing to continue in the study will follow the same active treatment protocol and follow the schedule of activities for Visits 1-10, specified in Appendix A.

SUBJECT DISCONTINUATION OR WITHDRAWAL

Subjects are free to discontinue study participation at any time upon request. Subjects who discontinue study treatment or active participation in the study will no longer receive treatment with Emsella Chair or sham. When a subject withdraws from the study, the reason(s) for withdrawal shall be recorded. Every effort will be made to obtain all end-of-treatment measures.

Additionally, subjects may be withdrawn from the study by the Principal Investigator (PI) for any of the following reasons:

- Subject cannot complete the full duration of treatment
- Subject cannot tolerate a minimum treatment level of 50% at any two treatment visits
- Development of any condition or AE that are clinically significant and may pose an additional risk to the subject
- The PI decides is in the best interest of the subject to withdraw from the study
- Subject is unable to follow Investigators' instructions and/or to comply with the study protocol

Replacements

Subjects who have been randomly assigned to receive treatment and who subsequently discontinue prematurely from the study may be replaced by another subject. The goal is to have 60 patients complete the entire study; 30 patients in each arm. Therefore, if/when subjects withdraw from the study prior to completing visit 9, an additional subject will be enrolled. Each subject will be assigned their own unique study identification number.

Subjects who fail to satisfy inclusion and exclusion criteria at screening may be rescreened at the discretion of the PI.

TABLE OF EVENTS

The table of events is included in Appendix A.

RISKS AND BENEFITS

Possible Risks

- Worsening of CPP
- Muscular pain
- Temporary muscle spasm
- Temporary joint or tendon pain
- Local skin redness
- Temporary increase of local circulation or blood flow
- Increased sensitivity during intercourse
- Heavier bleeding and/or cramping if treatments are administered during menstruation

Possible Risk of Breach of Privacy and Confidentiality

- There is a rare risk of breach of privacy and data confidentiality (release of information which personally identifies the subject). Confidentiality procedures will be strictly adhered to when transferring, managing, and analyzing study data. The subject will be assigned a unique study identification number and research information will be stored in a locked, secure cabinet in the Urology Research suite with access limited to authorized research personnel. Study data will be maintained in a password protected file on a shared network that can only be accessed by Urology research personnel.

Possible Benefits

- Improvement of chronic pelvic pain symptoms
- Improvement in quality of life

ELIGIBILITY CRITERIA

Inclusion Criteria

Each subject must meet all the following criteria to be enrolled in this study:

1. Able to read, understand, and provide written, dated, informed consent prior to screening, and be likely to comply with study protocol, including independently complete study questionnaires and communicate with study personnel about AEs and other clinically important information.
2. Females and males, 18 to 80 years of age, at screening
3. Self-reported CPP defined as pelvic pain that is non-cyclical and of at least 6 months duration and refractory to other treatments
4. Self-reported pelvic pain score ≥ 4 on VAS
5. Subject agrees not to start any new treatment for CPP (medication or otherwise) during the treatment and follow-up periods.
6. Subject agrees to maintain a stable dose all current medications throughout the treatment and follow-up period

For Females Only:

7. If of child-bearing age and female, agree to practice approved birth-control methods (oral contraceptives, condom barrier, injection, diaphragm or cervical cap, vaginal contraceptive ring, IUD, implantable contraceptive, surgical sterilization (bilateral tubal ligation), vasectomized partner(s))

Exclusion Criteria

A subject meeting any of the following criteria will be excluded from study participation:

1. Pelvic floor physical therapy, including muscle training and/or electrostimulation, in a clinical setting within 30 days prior to screening.
2. Pelvic floor trigger point injections, pudendal nerve block, or bladder hydrodistention within 30 days prior to screening
3. Subject weighs more than 330 pounds
4. Current UTI. If a subject has a confirmed symptomatic UTI at screening, per investigator's clinical judgment, they will be deferred from screening until treatment is completed, and may resume once symptoms have resolved
5. Pulmonary insufficiency, defined as difficulty breathing and fatigue, especially during exercise; chest pain, such as squeezing, pressure or tightness; the sensation of rapid or irregular heartbeat (palpitations); swelling of the legs or feet; dizziness or fainting; and/or bluish discoloration of the nails and/or lips (cyanosis)
6. Subject is currently receiving treatment for a malignant tumor that would interfere with study participation
7. Any condition that causes a lack of normal skin sensation to the pelvis, buttocks, and lower extremities
8. History of Hunner's lesion in the medical record
9. Major metal implants such as: metal plates, screws, joint replacements, implanted cardiac pacemakers, drug pumps, neurostimulators, electronic implants, copper intrauterine devices, defibrillators, and metal implants in the pelvic area. Patients with other metal implants will be evaluated by the investigator for inclusion in the study.
10. Subject has a piercing between the waist and knees and is not willing to remove it before each treatment
11. Subject has used the BTL EMSELLA device previously
12. Currently participating in an investigational study that may impact study results or previously received an investigational drug or treatment within 30 days of the Screening Visit
13. Current or history of any physical condition that, in the investigator's opinion, might put the subject at risk or interfere with study results interpretation

For Females Only:

14. Pregnant, or planning to become pregnant, at screening or anytime throughout the study period

STATISTICAL ANALYSES

Sample Size Calculation

We evaluated the difference in VAS decrease (primary outcome) between the Emsella Chair group and the Sham group that would be detectable with 80% power and assuming a 5% significance level. We used Pass 16 to determine the effect size detectable when testing for the between-group difference in the post-pre difference in a score. We assumed that the standard deviation of VAS would be 2.5 cm both at baseline and at visit 9. We varied the within-subject correlation between pre- and post-scores from 0.1 to 0.8. This correlation describes the extent to which subjects show similar post-pre differences, with a correlation of 0.2 being observed when there is relatively little similarity in subjects' post-pre differences. Based on these assumptions, we would have 80% power to detect a difference of 2.3 cm between the decrease in VAS in the Emsella Chair group and the Sham group, given a sample size of 30 subjects per arm and a within-subject correlation of 0.2. In this scenario, we could detect a 3.3 cm decrease in VAS in the Emsella chair group if the Sham group shows a 1.0 cm decrease in VAS. The difference in the VAS decrease detectable decreases as the within-subject correlation increases (Figure 2).

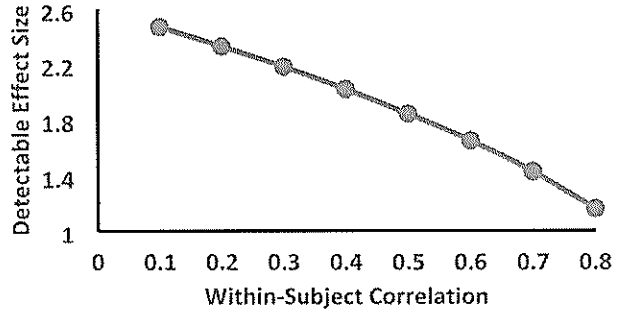

Figure 2 – The difference in the decrease in VAS between the Emsella Chair and Sham groups detectable with a total sample size of 60.

Analysis Sets

Data analysis will be performed on a full analysis set (FAS), a per protocol set (PPS), an intent-to-treat (ITT) set, a durability set (DS), and a safety analysis (SA) set.

The FAS will be used for the primary analysis. The FAS will consist of all randomized subjects who receive at least one treatment session and have at least 1 post baseline primary efficacy assessment (VAS score). All analyses using the FAS will group participants according to randomized treatment.

The PPS will be used for a supportive analysis and will be defined as all subjects included in the FAS who do not have any significant protocol deviations. All analyses using the PPS will group subjects according to the actual treatment received.

The ITT set will consist of all randomized subjects who receive at least one treatment session. All analyses using the ITT set will group subjects according to randomized treatment. Subjects who do not have any post-baseline assessments will be treated as non-responders for ITT analyses.

The DS set will consist of all subjects who receive all eight treatments and complete the 12 week study visit.

The SA set will include all safety parameters (including AEs). The SA set will be utilized to summarize treatment safety.

Methods

Before unblinding, a separate statistical analysis plan (SAP) will be finalized, providing detailed methods for all endpoints. In general, summary statistics (n, mean, standard deviation, median,

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minimum and maximum values for continuous variables, and number [%] of subjects in each category for categorical variable) will be provided by treatment group and visit. Source data for summary tables and statistical analyses will be presented as subject data listings.

The primary efficacy period is defined as baseline (Day 0) through Week 8 (4 weeks after completing treatment). Change from baseline and determination of responder rate status will be between baseline and visits through Week 8.

Analysis of the Primary Efficacy Endpoint
The primary analysis will be conducted on the primary endpoint using the VAS. Change in VAS will be evaluated using ordinal regression methods for continuous outcomes. We will include the following effects in the model: group (Emsella chair vs Sham), time, the interaction of group and time, and subject. The test of interest for this analysis will be the group/time interaction. The analysis of change in VAS can be problematic if many subjects report initial VAS at the maximum or final VAS at the minimum. As such, we will also consider categorizing subjects as to whether they showed at least a 50% decrease in VAS from baseline. We will use a 5% significance level and 95% confidence intervals.

Analysis of Secondary Efficacy Endpoints
For all secondary efficacy endpoints, we will use 0.42% significance level and 99.6% confidence intervals based on a Bonferroni adjustment for 12 tests. All secondary efficacy endpoints are pain scales. For each endpoint, we use either ordinal regression for continuous outcomes or cumulative probit models depending on the scale of the given instrument. Regardless of the specific type of model, we will include the following effects in the model: group (Emsella chair vs Sham), time, and the interaction of group and time. Models for ordinal regression of continuous outcomes will include subject as a fixed effect, while cumulative probit models will include a random intercept for subject.

Durability of the treatment effect will be examined in the DS for this efficacy endpoint.

Missing Data
We will use complete case analysis for all efficacy endpoints as long as the percent of missing data is less than 5%. If the proportion of missing data is greater than 5%, we will evaluate the potential missing data mechanism including examining associations between baseline characteristics and the probability of missing. Importantly, we will examine if dropout rates differ between the groups, as well as whether dropout is related to baseline patient reported pain and discomfort VAS score. Provided there is no evidence for data being missing not at random, we will use multiple imputation for all missing data. In this scenario, responder status will be based on the imputed patient reported pain and discomfort VAS score at Week 8.

Safety Analyses
All safety parameters (including AEs) will be summarized using the SA set. No formal hypothesis testing will be performed.

All AEs will be coded using the latest version of MedDRA. All treatment emergent adverse events (TEAEs) will be summarized and presented in the listings by the number of subjects reporting an event, the percentage of subjects with that event, the number of events, and the grade, duration, and relationship to treatment. Percentages will be based on the number of subjects who received each treatment during the study. TEAEs are defined as events that

emerge during treatment, having been absent pretreatment, or worsen relative to the pretreatment state.

DATA and SAFETY MONITORING PLAN

Ongoing safety monitoring will be performed by the study staff, including the Principal Investigator (PI) and co-investigators. The PI will have ultimate responsibility of assuring subject safety. Safety issues will also be addressed in the annual reports to Beaumont's Investigational Review Board (IRB).

Additional data safety monitoring procedures include:

- Research Administration's Clinical Research Quality and Process Improvement Program (CRQIP) will perform in-house monitoring of the first subject enrolled after the completion of Visit 1
- An audit of the study records after the first 10 subjects are enrolled, at the halfway point of enrollment, and at the end of the study by an RN in the Urology Research Department that is not directly involved with the research study. Additional monitoring may occur as needed. This will be done to ensure the safety of subjects and lack of significant adverse effects.

As an on-going plan, any adverse effects (prolonged irritation, hemodynamic changes, significantly worsened pain, or other deemed significant by clinicians) will be reported to the study staff and then to the PI at the time of the event. Adverse events, serious adverse events, and unanticipated problems not listed in the risks section of this protocol will be reported per IRB guidelines.

Subject records will be reviewed to verify case report form (CRF) completion and delinquencies, and capture protocol deviations and frequency of unanticipated problems/adverse events. To identify, evaluate, and prevent adverse events, the total number of events will be reviewed, as well as the details of each event, including visit number and severity. Data will be reviewed to identify trends and possible concerns. Enrollment data will direct recruitment efforts and assist in study planning.

The overall objectives of routine monitoring are to:

- Document clinical study progress.
- Document that the protocol and associated forms are current.
- Obtain and review current clinical data, reports, and source documents.
- Review the overall study status including verification of the study files. All required documents and records should be accurate, complete, and current.
- Confirm that all subjects have signed the informed consent form.
- Confirm that all enrolled subjects have met the eligibility criteria.
- Verify accuracy of transferring data from source document(s) to the CRFs to the database.
- Confirm complete, accurate, and timely event reporting.
- Confirm adequacy of staff and facilities.
- Review communication records.
- Verify identification and reporting of protocol violations.

Outcomes of all scheduled and unscheduled study monitoring will be documented. Follow-up action items will be included in the report. The monitoring summary report will be forwarded to the PI and research coordinator.

Quality Control and Quality Assurance (QC/QA)

The PI or designee has primary responsibility for QC/QA activities of the data. Beaumont's Research Institute also audits investigator-initiated studies to ensure compliance with consent processes and reporting requirements. The key QC/QA activities for the study will be:

- Clearly formatted and carefully constructed CRF;
- Sign-Off Procedures for all CRFs;
- Verification of subject eligibility at each visit

A database will be created utilizing RedCap or MS Excel software. Only designated study personnel will have access to the database, which will be stored on the Urology Research Department's shared drive. Access to the computerized system will be password protected. To ensure accuracy of data entry, database entries will be cross-checked against source documents. The shared drive is backed up nightly to ensure minimal data loss, even in the most catastrophic system failure. The database will be active until all study visits are completed, final monitoring activities have been conducted, and all data queries have been resolved. After that time, the database will be locked, prohibiting any changes to the data.

All study records, including both paper and electronic, will be stored in accordance with all federal and institutional requirements, including, but not limited to, the HIPAA Privacy Rule, the Food and Drug Act, and Medicare policy. The stored data will be kept in a secure, protected manner. All records will be retained, at a minimum, for eleven years beyond study completion.

SUMMARY of EXISTING STUDY DATA

The BTL Emsella has received 510(k) approval as a "nonimplanted electrical continence device" and is currently being used as a non-invasive treatment for SUI. The limited number of studies on this HIFEM technology have focused on its effects on stress, urge, and mixed urinary incontinence as well as quality of life. A white paper, entitled "HIFEM™ Technology Can Improve Quality of Life of Incontinent Patients" summarizes the results of a pilot study, which enrolled and treated 30 women with stress, urge or mixed urge incontinence [29]. Quality of life (QOL) was assessed after the women received 6 treatments, and again at 3 and 6 months post treatment. Ninety-five percent (95%) of the women reported improvement in QOL after treatment completion. Results were maintained over the follow-up periods. Additionally, 67% of the women decreased or eliminated the use of incontinence pads. Similar results were seen in studies by Samuels, Alinsod, Cidranes and Blanco [30, 31, 32, 33]. Additionally, advance ultrasound (elastography) revealed elastographic changes, indicating the improvement in pelvic muscle tone in all the subject's post-treatment.

These prior studies utilize the HIFEM technology to induce maximal muscle contraction, essentially simulating Kegel exercises and strengthening the pelvic floor to reduce SUI. In patients with CPP, the pelvic floor has already gone into spasm, causing hypertonicity and pain. With alternate settings of high frequency and low intensity, HIFEM technology can induce submaximal stimulation, whereby the muscle fibers are stimulated, but do not contract. It may be possible to fatigue these overactive muscle fibers, in a manner similar to PFPT. This could lead to muscle relaxation and improvement in pelvic pain. To our knowledge, no studies to date have explored HIFEM for this purpose.

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APPENDIX A

Table of Events

	Screening	Week 1		Week 2		Week 3		Week 4		Week 8 [g]	Week 12	Week 13		Week 14		Week 15		Week 16		Week 20	Week 24
Visit	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
Visit Window [a]		±14 days								±7 days	±7 days	±12 weeks								±7 days	±7 days
Informed consent	X																				
Eligibility criteria review	X	X																			
Medical history & Demographics	X																				
Height and weight	X																				
Urine pregnancy test [b]	X	X		X		X		X				X		X		X		X			
UA dipstick (with culture as needed)[c]	X									X										X	
Gynecologic Pelvic examination [d]	X									X										X	
Digital rectal examination [e]	X									X										X	
Randomization		X																			
Treatment: Emsella or Sham		X	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X		
Blinding assessment									X												
Pain VAS	X									X	X									X	X
Pain VAS pre/post treatment		X	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X		
PGI-I			X		X		X		X	X	X		X		X		X		X	X	X
PGI-S	X		X		X		X		X	X	X		X		X		X		X	X	X
FSFI (females), BSFI (males), BDI, OAB-q, ICSI-PI, GAD7, MPQ, PCS	X									X	X									X	X
GRA										X	X									X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse event(s)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Un-blinding (Sham group is offered active treatment after un-blinding) [f]											X										

[a] Visit windows may be extended due to scheduling challenges, with the goal of completing all 8 treatment visits within a 6-week window.

[b] Only women of child-bearing potential will be required to have a urine pregnancy test

[c] UA and C&S may be repeated if the patient is symptomatic at any other time during visits 1-8, per clinician judgment

[d] Female patients will undergo a gynecologic pelvic examination to assess levator muscle tenderness

[e] Male patients will undergo a digital rectal examination to assess levator muscle tenderness

[f]Patients that are originally randomized to the sham treatment will be offered active treatment after the secondary endpoint visit is completed. Those patients who wish to undergo active treatment will then follow the same schedule of events as above, for visits 1-10, except for the validation of blinding questionnaire.
[g]The primary endpoint for follow up evaluation will be 4 weeks after completion of the last treatment (week 8 of the study). The durability endpoint is 4 weeks following the primary endpoint (week 12 of the study).

APPENDIX B

Data Collection Tools

Visual Analog Scale
The VAS is a self-administered questionnaire to assess overall pain and discomfort. Subjects indicate their average pain score during treatment on a straight line from 0 (no pain) to 10 (most severe pain imaginable). Extensive research supports the validity the VAS for assessment of pain intensity [34].

Patient Global Impression of Severity
The PGI-S is a global rating of subject-reported impression of the severity of a condition using a 4-point scale. Validity of the PGI-S has been established for application in SUI, pelvic organ prolapse, and other non-urologic disease [35].

Patient Global Impression of Improvement
The PGI-I is a global rating of subject-reported impression of improvement in a specific medical condition using a 7-point scale. Validity of the PGI-I has been established for application in SUI, pelvic organ prolapse and other non-urologic disease including pain [35].

Female Sexual Functioning Index
The FSFI is a self-administered questionnaire to assess overall sexual experience that consists of 19 questions that are scored from 0 to 5. The scale contains 6 domains: desire, arousal, lubrication, orgasm, satisfaction, and pain. The FSFI total score is a weighted average of the 6 domains with each contributing a maximum of 6 points to the total (maximum score of 36) [36].

Brief Sexual Function Inventory
The BSFI is a self-administered questionnaire to assess male sexual function. It includes the following domains; sexual drive (two items), erection (three items), ejaculation (two items), perceptions of problems in each area (three items), and overall satisfaction (one item). The BSFI is scored on a 5-point scale, where the scores for each domain are computed separately from one another [37].

Beck Depression Inventory
The BDI is a 21-question multiple-choice self-report inventory, and one of the most widely used psychometric tests for measuring the severity of depression. It is composed of items relating to symptoms of depression such as hopelessness and irritability, cognitions such as guilt or feelings of being punished, as well as physical symptoms such as fatigue, weight loss, and lack of interest in sex. Subjects that score >30 at any time throughout the trial may be referred for psychological evaluation but may continue study participation.

Overactive Bladder Questionnaire-Short Form (OAB-Q)
Since both overactive bladder and IC/BPS share urinary urgency and frequency symptoms, this validated measure will evaluate additional aspects of symptoms associated with IC/BPS. The OAB-Q consists of symptom severity and health related quality of life scales (HRQOL) [38]. Statistically significant correlations have been found between the OAB-q SF scales and other patient reported outcomes instruments. For example, higher levels of depressive symptoms as

measured by the CES-D were linearly related to higher levels of Symptom Bother (r 0.31, P<0.0001) and lower levels of HRQL on the OAB-q SF (r 0.35, P<0.0001). Both the Symptom Bother and HRQL scales easily differentiated between Control without overactive bladder (OAB), Continent patients with OAB and incontinent OAB patients (P<0.0001). These results provide evidence that the Symptom Bother and HRQL short-forms developed in this study are valid and can be used in a clinical or research context to differentiate OAB patients from normal, healthy individuals.

Interstitial Cystitis Symptom Index and Problem Index (ICSI-PI)
The IC symptom and problem indices measure urinary and pain symptoms and assess how problematic symptoms are for patients with IC/PBS. Psychometric performance of both instruments is good, with the symptom index demonstrating excellent ability to discriminate characteristics between patients and controls.

Generalized Anxiety Disorder Questionnaire (GAD-7)
The GAD-7 questionnaire is a 7-item validated scale to assess generalized anxiety disorder. On the GAD-7, patients are grouped by GAD score 0-7 and 8+ which suggests no anxiety disorder and probable anxiety disorder, respectively.

McGill Pain Questionnaire (MPQ)
The McGill Pain Questionnaire can be used to evaluate a person experiencing significant pain. It can be used to monitor the pain over time and to determine the effectiveness of any intervention [39]. It was developed at McGill University in Montreal Canada and is widely used in pain research.

Pain Catastrophizing Scale (PCS)
Pain catastrophizing is the tendency to describe a pain experience in more exaggerated terms than the average person, to ruminate on it more (e.g., "I kept thinking 'this is terrible'"), and/or to feel more helpless about the experience ("I thought it was never going to get better"). People who report a large number of such thoughts during a pain experience are more likely to rate the pain as more intense than those who report fewer such thoughts. The PCS is a validated measure of rumination, magnification, and helplessness related to pain. The PCS has been shown to have adequate to excellent internal consistency (coefficient alphas: total PCS = .87, rumination = .87, magnification= .66, and helplessness = .78) [40].

Global Response Assessments (GRA) for Pain and QOL
GRA evaluate the patients' perceptions of overall improvement in symptoms on a 7-point scale (markedly worse, to markedly improved). GRAs have been widely used as primary endpoints in IC/BPS trials [41], and have been correlated with voiding diary records [42].

Validation of Blinding Questionnaire
The validation of blinding questionnaire will be given to evaluate the patients' perception of stimulation received. Patients will be asked if they received active stimulation or sham stimulation. Patients will also be asked how confident they are in their answer, this is measured on a scale from 1-5 (1 is not confident at all and 5 is completely confident).