PROTOCOL TITLE:

INSTRUCTIONS[i]:

- *Use HRP-503 - TEMPLATE PROTOCOL to prepare a document with the information from following sections.*
- *Depending on the nature of your study, some sections may not be applicable to your research. If so mark as "NA." For example, research involving a retrospective chart review may have many sections with "NA." For subsections, like 1.x or 8.x, you can delete it if it's not applicable.*
- *When you write a protocol, keep an electronic copy. You will need to modify this copy when making changes.*
- *As you are writing the protocol, remove all instructions in italics so that they are not contained in the final version of your protocol.*
- *For submission of a protocol specific to a participating Site as part of a Multi-Site Study, use HRP-508 – TEMPLATE - SITE SUPPLEMENT*

PROTOCOL TITLE:

Non-invasive brain neuromodulation in men for management of incontinence after prostate treatment: a proof-of-concept study

PRINCIPAL INVESTIGATOR:

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VERSION NUMBER/DATE:

Version 4/ 10 Sept 2026

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
1	5/12/2026	Expanded inclusion to all prostate treatments and any UI type; adjusted age range to 22-80; updated safety endpoints per FDA.	No
2	6/10/2026	Added IDE#, Increased subject compensation amount	Yes
3	9/10/2026	Adding continent control cohort (n=10) **that will only receive non invasive MRI (visit 1, 2, and 3 only) without any other intervention or stimulation**, added Aim 3 with hypothesis and case-control secondary endpoints, clarified Visit 3 (cap	Yes

		measurements/markings for neuronavigation setup-optional) and Visit 4 (neuronavigation with resting motor threshold determination), updated Schedule of Events	

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1.0 Study Summary

Protocol Information	Description
Study Title	Non-invasive brain neuromodulation in men for management of incontinence after prostate treatment: a proof-of-concept study
Study Design	Prospective, Randomized, Proof-of-Concept Clinical Trial.
Primary Objective	Assess the safety, tolerability, acceptability, and procedural feasibility of performing pelvic supplementary motor area (pSMA)-targeted repetitive transcranial magnetic stimulation (rTMS), pelvic floor electromyography (EMG), and functional Magnetic Resonance Imaging (fMRI) in men with incontinence after prostate treatment (IPT) and continent controls (CC)
Secondary Objective(s)	Evaluate the physiological and neurofunctional effects of excitatory (high-frequency) and inhibitory (low-frequency) rTMS on pSMA activity and pelvic floor muscle (PFM) tone.
Research Intervention(s)/ Investigational Agent(s)	Repetitive Transcranial Magnetic Stimulation (rTMS) and Neuronavigation System
IND/IDE #	IDE# G260107
Study Population	Adult males with any urinary incontinence (UI) after prostate treatment and continent men after prostate treatment (CC)
Sample Size	23
Study Duration for individual participants	6-8 weeks
Study Specific Abbreviations/ Definitions	**KEY ABBREVIATIONS**: adverse events (AEs), Acceptability of Intervention Measure (AIM), blood-oxygen-level-dependent (BOLD), chronic pelvic pain (CPP), continent controls (CC), electromyography (EMG), functional Magnetic Resonance Imaging (fMRI), high frequency (HF), incontinence after prostate treatment (IPT), low frequency (LF), lower urinary tract (LUT), Montreal Cognitive Assessment (MoCA), overactive bladder (OAB), pelvic muscle floor (PFM), pelvic floor muscle training (PFMT), pelvic Supplementary Motor Area (pSMA), repetitive Transcranial Magnetic Stimulation (rTMS), urinary incontinence (UI), urinary tract infection (UTI) .

2.0 Objectives

Aim 1: Assess th**e safety, tolerability, acceptability, and procedural feasibility** of performing SMA-targeted rTMS, pelvic EMG, and fMRI in men with Incontinence after Prostate treatment (IPT). We hypothesize that rTMS will be safe, well-tolerated, and feasible in men with IPT. Safety and tolerability will be assessed by monitoring and grading adverse events (AEs). Acceptability will be evaluated with a validated questionnaire. Feasibility will be evaluated using predefined benchmarks for recruitment, retention, and data completeness; defined as >80% completion of planned sessions.

Aim 2: Evaluate the **physiological and neurofunctional effects of excitatory** (high-frequency) and inhibitory (low-frequency) rTMS on pSMA activity and PFM tone. We hypothesize that high-frequency (HF) rTMS will increase pSMA activity and reduce PFM tone, while low-frequency (LF) rTMS will decrease pSMA activity and increase PFM tone. pSMA activity will be assessed by changes in blood-oxygen-level-dependent (BOLD) signal at baseline and post-treatment fMRI. PFM tone will be assessed by pelvic EMG amplitudes.

Aim 3: Compare baseline pSMA activity (BOLD signal on fMRI) and functional connectivity between continent post-prostate-treatment controls and men with IPT. We hypothesize that continent controls (CC) will demonstrate intact pSMA-continence network activation and connectivity, whereas men with IPT will display aberrant baseline pSMA functional connectivity.

3.0 Background

I. SIGNIFICANCE

Prostate cancer is the most common cancer among men in the United States, and radical prostatectomy remains a primary treatment option. Incontinence after prostate treatment (IPT), particularly following radical prostatectomy, is a persistent and debilitating condition affecting up to 25% of men at 10 years.[1-2] IPT is primarily driven by sphincteric insufficiency, impaired pelvic floor coordination, and disrupted neuromuscular control.[3] The impact of IPT extends beyond urinary leakage. It is associated with significant psychological distress, functional impairment, social isolation, and reduction in quality of life.[4]

A. The Missing Link: Central Neural Control

Traditionally, IPT has been viewed as a peripheral issue and existing therapies target peripheral structures (PFM, urethral sphincter, or urethral support). However, continence is not merely mechanical; it is a complex neuromuscular function relying on coordinated input from the central nervous system. With advances in functional neuroimaging, we have gained insight into brain control over lower urinary tract (LUT) function.[4-6] The functional demands of urinary storage and continence rely on tightly integrated interactions across the LUT, spinal cord, and supraspinal centers including the pelvic supplementary motor area (pSMA), prefrontal cortex, cingulate cortex, and insula.[6]

Dysfunction of the SMA brain region has been described in PFM disorders such as chronic pelvic pain (CPP), overactive bladder (OAB) and urinary incontinence.[7-9] Neuroimaging studies demonstrate alterations in SMA gray matter volume, white matter integrity, local activity, and periaqueductal gray to SMA interaction in patients with CPP and incontinence.[7] The degree of SMA dysfunction may predict treatment response, underscoring its role in PFM activation and continence control. Prior studies have demonstrated that the pSMA contains motor neurons that directly modulate PFM activity.[7,10]

- If pSMA activity could be modulated in a way that increases PFM activity, this mechanism can augment existing therapies for IPT when treatment response is inadequate.

B. Current Management of IPT and their Limitations

Pelvic Floor Muscle Training (PFMT) is a safe treatment with minimal side-effects that is readily accepted by patients. However, it relies heavily on patient compliance and is time consuming and has limited benefit for severe urinary incontinence.[1,11]

Other non-invasive options with modest effectiveness include behavioral therapy (timed voiding), use of pads, penile clamps, and condom catheters.

Male Sling is a surgical option where mesh tape is placed to support the urethra in men without a history of radiation therapy.[12] It is limited by variable success rates (only 62% of patients in 15 cohort studies achieved cure) and is generally reserved for mild to moderate incontinence.[1]

Artificial urinary sphincter is the gold standard for surgical treatment of male stress urinary incontinence (SUI). It involves the implantation of a cuff around the urethra, a pump in the scrotum and a pressure regulating balloon. It has long-term success rates ranging from 70 to 90%.[1,13] However, it is invasive and carries risks of infection, urethral erosion, mechanical failure and the need for revision surgery.[14]

- Currently, all available therapies for IPT target peripheral structures. To date, neuromodulation of continence pathways remains unexplored in men with IPT. This project represents the first effort to directly modulate the pSMA in this population using rTMS.

II. INNOVATION

- Brain neuromodulation for treatment of IPT is innovative as no current IPT treatment therapy targets the cortical networks responsible for neuromuscular coordination of pelvic floor and continence mechanism.
- Application of rTMS for IPT is a novel concept. While rTMS is established for treatment of depression and stroke, and in urology, several trials have demonstrated improvement in CPP, LUT control in neurogenic lower urinary tract dysfunction and OAB, there are no prior studies evaluating rTMS for IPT.

Evidence to support rTMS

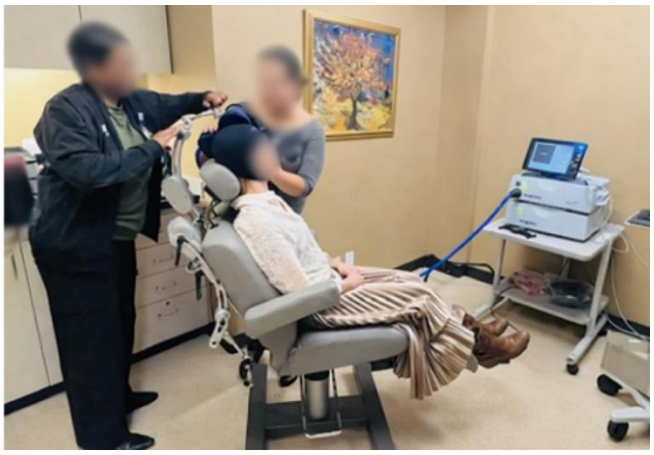


Figure 1: rTMS treatment set up

rTMS is a non-invasive, centrally acting neuromodulation technique in which an electromagnetic coil is held over the scalp to deliver a rapidly pulsed magnetic field to the cortex to modulate neurons, Figure 1. This method allows for effective modulation of cortical neurons without the need for anesthesia or significant side effects. rTMS is commonly used in brain mapping, modulating cortical excitability, and treating conditions like depression, migraines, and obsessive compulsive disorders.[15-20] rTMS can be delivered continuously with low frequency (1 Hz) to inhibit brain activity or in bursts with a high frequency (5–10 Hz) to enhance it.[21] rTMS can modulate cortical excitability and induce long-lasting neuroplastic changes when applied to cortical regions corresponding to pelvic floor.[22]

- Previous studies have demonstrated the effectiveness of using rTMS to inhibit the SMA in patients with MS, Parkinson's disease and CPP.[7, 23-25]

In our institution's pilot clinical trial utilizing rTMS in multiple sclerosis patients with voiding dysfunction, no treatment-related adverse effects were reported.[27] rTMS effectively modulated brain regions involved in the voiding phase of the micturition cycle with clinical improvement in bladder emptying and perceived improvement in patients' urinary incontinence symptoms.

Rationale for this proposed study

While prior studies demonstrate the efficacy of pSMA modulation in conditions like CPP and OAB, these disorders are fundamentally different from IPT. CPP and OAB are often characterized by sensory dysregulation and hypertonicity. In contrast, IPT manifests primarily as SUI, resulting from sphincteric incompetence and impaired neuromuscular control. Prior studies, although limited by size, have demonstrated the effectiveness of rTMS in modulating pSMA activity and PFM tone. In a study with chronic pelvic pain patients by Kutch and Rodriquez, **excitatory HF-rTMS increased pSMA activity and decreased PFM tone, while inhibitory LF-rTMS decreased pSMA activity and increased PFM tone**.[7] Similarly, preliminary results by Dr. High at our institution show that when LF-rTMS was applied to the pSMA in OAB patients, it increased PFM tone.[26]

However, the baseline cortical state of men with IPT is unknown. It remains unclear whether the pSMA in these men requires excitation (HF) or inhibition (LF) rTMS to increase PFM tone. The lack of data on IPT prompts us to ask the question: Can targeted cortical modulation of the pSMA improve PFM tone and improve continence control in men with IPT? This proof-of-concept study addresses this gap by first establishing the safety and feasibility of rTMS in this patient population and directly comparing the physiological effects of HF versus LF stimulation, establishing the necessary evidence to target the correct neural pathway for future rehabilitation strategies.

Furthermore, studying continent men after prostate treatment controls can help define the normative pSMA/PFM reference to interpret whether IPT men need excitatory vs inhibitory rTMS.

4.0 Study Endpoints

Primary endpoints: Safety, Tolerability, Acceptability and Feasibility
(1) Recruitment/retention rate: Proportion of participants enrolled in the study and proportion lost to follow-up.
(2) Acceptability of intervention (rTMS): Participant acceptability will be evaluated using the Acceptability of Intervention Measure (AIM) questionnaire. Participants' perspectives on the feasibility and practicality of rTMS into routine care will be captured using the AIM questionnaire.
(3) Safety: Incidence of all patient- or physician-reported AEs occurring throughout the study duration.

Secondary endpoints: Physiological and Neurofunctional Effects
(1) pSMA activity will be assessed by changes in BOLD signals between baseline and post-treatment fMRI.
(2) PFM tone will be assessed by changes in pelvic EMG amplitudes after each corresponding rTMS pulse.
(3) Differences in baseline pSMA BOLD signal and functional connectivity during natural bladder filling between IPT and CC

5.0 Study Intervention/Investigational Agent

We will use Repetitive Transcranial Magnetic Stimulation (rTMS) and Neuronavigation System for this trial. The Magstim Rapid^2 system is the most commonly used magnetic stimulation system for rTMS clinical studies and therapeutic investigations, capable of selectively inducing, modulating or suppressing neuronal activity. This system is capable of high frequency repetitive protocols for cortical stimulation reaching frequencies of up to 36Hz (11Hz at max power). This rTMS device will be used along with the D70 Alpha Coil package, which includes an active coil ideal for focal rTMS.

We are utilizing the StimGuide navigation system (currently available at the HMRI) to accurately target the proposed regions of interest. This neuronavigator is equipped with 4 positioning parameters (aligning contact, XY location, tilt, and rotation) allowing for more precise and consistent positioning of the coils during stimulation sessions.

6.0 Procedures Involved

Study design rationale: There are currently no clinical trials evaluating the use of rTMS for IPT. While rTMS has been used for other neurological and urological conditions (e.g., depression, OAB, CPP), its application in IPT is a novel frontier. A proof-of-concept study is necessary to establish both safety and feasibility and biologic plausibility; specifically, whether cortical modulation of the pSMA can influence PFM tone in this specific population. This study is designed as a randomized, single-session, mechanistic trial to identify which stimulation frequency (excitatory vs inhibitory) produces the desired physiological signal (increased PFM tone) before advancing to guide design of a randomized controlled trial of TMS versus sham (in the future).

Sample size and power calculation:

The proposed sample size of 20 (10 IPT subjects and 10 CC) for this proof-of-concept study considers the feasibility of recruitment with sufficient preliminary numbers to evaluate safety, and to obtain variance and effect size estimates that will inform design and powering of a

subsequent pivotal study. We anticipate a screen failure or technical attrition rate of approximately 17% (3 subjects). This buffer is essential to ensure the study reaches its primary aims with a full dataset.

Schedule of events

Participants will attend a maximum of 5 visits for this study with the last visit being virtual. The first two visits can be combined based on the participant's preference. An overview of each visit can be found in the flowchart (Figure 2). Continent control flowchart in Figure 3 (they will not receive any stimulation)

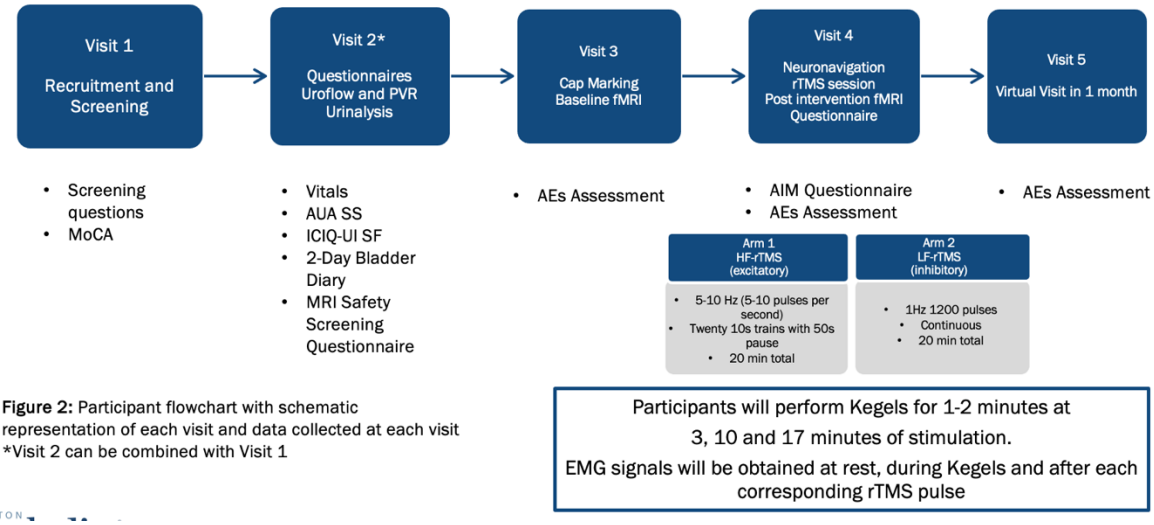


Figure 2: Participant flowchart with schematic representation of each visit and data collected at each visit
*Visit 2 can be combined with Visit 1

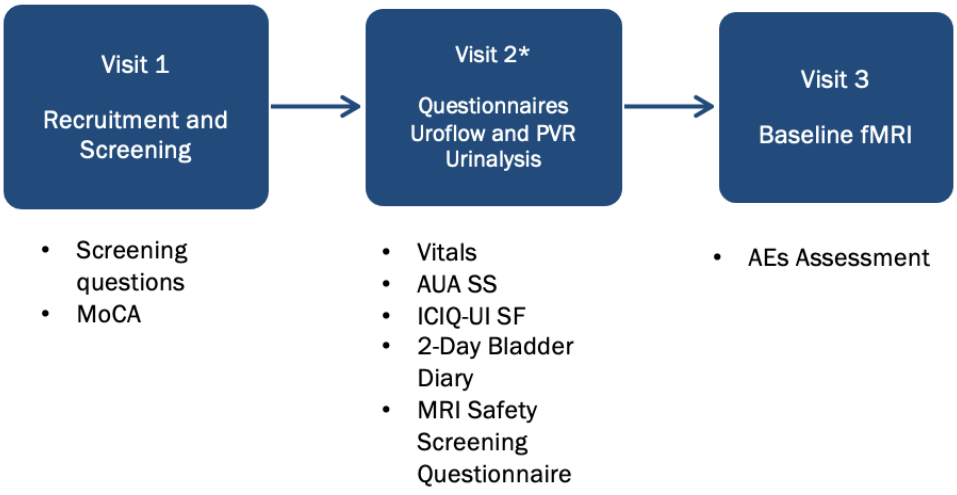


Figure 3: Continent Control Participant flowchart with schematic representation of each visit and data collected at each visit
*Visit 2 can be combined with Visit 1

Recruitment and Screening (Visit 1): Patients' status post prostate treatment with incontinence will be identified as potential candidates. Patients' status post prostate treatment with continence

will be identified as CC. At the screening visit, our research coordinator will offer participants comprehensive information about the study. Potential participants will receive standardized educational materials, including one one-page handout with standardized PFMT, a pamphlet and video describing the study. This ensures that all participants receive consistent, unbiased information. After obtaining consent, Montreal Cognitive Assessment (MoCA) will be administered by study personnel. Participants may decide to complete questionnaires, uroflow, PVR and urinalysis at this visit or at a subsequent visit (Visit 2). Questionnaires include American Urological Association Symptom Score (AUA-SS), International Consultation on Incontinence Questionnaire -Urinary Incontinence Short Form (ICIQ-UI SF and MRI Safety Screening Questionnaire. They will also receive a 2-day Bladder diary to complete.

Baseline scan and neuronavigation setup (Visit 3 for IPT cohort): Cap measurements and markings are made for neuronavigation setup (optional). Images during a natural bladder filling protocol will be obtained using either a 3T or 7T MRI scanner depending on their medical history and safety requirement for potential body implants that could be contradictory to the ultra-high field MRI (7T). After patients undergo an anatomical and functional brain MRI scan, the pSMA location will be determined using their Montreal Neurological Institute coordinates for the individual through the neuronavigation system. All adverse events (AEs) will be documented.

Baseline scan (Visit 3 for CC cohort): No cap measurements or cap markings are obtained, as no neuronavigation or rTMS is performed. Images during a natural bladder filling protocol will be obtained using either a 3T or 7T MRI scanner depending on their medical history and safety requirements for potential body implants that could be contraindicated for the ultra-high-field MRI (7T). All adverse events (AEs) will be documented. **This completes study participation for CC cohort; they do not undergo Visit 4 (neuronavigation, motor threshold determination, or rTMS/EMG) or the Visit 5 follow-up.**

Intervention (Visit 4): Using cap markings if obtained during optional cap marking, the rTMS probe will be positioned using tracking via the BrainSight neuronavigation system. The resting motor threshold will be determined, and stimulus strength will be set to 70–80% of the resting motor threshold. The patients will be randomized to two groups in a 1:1 ratio. Group 1: HF-rTMS) and Group 2: LF-rTMS. Stimulus strength corresponding to 70-80% of the resting motor threshold. The protocol for HF-rTMS will consist of twenty 10 second trains at 5-10Hz (5-10 pulses per second) with a 50 second pause in between trains, for a total of 20 minutes for the HF-rTMS section of the stimulation. The protocol for the LF-rTMS will consist of 1Hz continuously for 20 minutes (1,200 pulses). Parameters were derived from our institutions' recent rTMS on OAB patients.[26] Participants will be asked to perform Kegel exercises at minute 3, 10 and 17 for 1-2 minutes each during stimulation. EMG signals will be obtained from perineal surface electrodes at rest and during Kegels and after each corresponding rTMS pulse. After the rTMS intervention, participants will return for a follow-up fMRI scan. Participants will then complete the AIM questionnaire, and AEs will be documented.

Follow-up (Visit 5): A virtual visit will be conducted at 1 month to review AEs.

Primary endpoints: Safety, Tolerability, Acceptability and Feasibility
(1) Recruitment/retention rate: Proportion of participants enrolled in the study and proportion lost to follow-up.
(2) Acceptability of intervention (rTMS): Participant acceptability will be evaluated using the Acceptability of Intervention Measure (AIM) questionnaire. Participants' perspectives on the feasibility and practicality of rTMS into routine care will be captured using the AIM questionnaire.

(3) Safety: Incidence of patient- or physician-reported AEs related to the procedure, device, and/or stimulation throughout the study duration.
Secondary endpoints: Physiological and Neurofunctional Effects
(1) pSMA activity will be assessed by changes in BOLD signals between baseline and post-treatment fMRI.
(2) PFM tone will be assessed by changes in pelvic EMG amplitudes after each corresponding rTMS pulse.
(3) Differences in baseline pSMA BOLD signal and functional connectivity during natural bladder filling between IPT and CC

Safety monitoring plan and hard stops:
Participants will fill out questionnaires after each treatment session to identify any potential adverse events related to rTMS. There is level B evidence "probable effective/ineffective" regarding rTMS for fibromyalgia, chronic post-stroke non-fluent aphasia, Parkinson's disease depression and motor impairments, motor recovery post-acute stroke, lower limb spasticity in MS, and post-traumatic stress disorder. Moreover, neuronavigation systems have become the norm for achieving precise and accurate positioning of TMS and are frequently utilized alongside TMS for tumor mapping in neurosurgical preplanning. If a participant experiences discomfort with any of the interventions (fMRI, Neuronavigation, rTMS treatment), these symptoms will be evaluated and remediated immediately. Adverse events will be reported and we will discuss such events with our safety monitoring team and IRB and will proceed according to their recommendation. Please see section 18 (Provisions to Monitor the Data to Ensure the Safety of Subjects) for details on the detailed hard stops for this project.

Data Collection
The following data will be collected at each time point.

	Recruitment and Screening (Visit 1)*	**Questionnaires (Visit 2)**	**Cap Measurement and Markings (Visit 3-optional)**	**Baseline Imaging fMRI Scan (Visit 3)**	**Neuronavigation (Visit 4)**	**rTMS session with follow up fMRI (Visit 4)**	**Follow-up Virtual Visit (Visits 5)**
Patient History	X						
Inclusion/Exclusion Review	X						
Consent for Study	X						
Montreal Cognitive Assessment (MoCA)	X						
Vital Signs		X					
Uroflow and Post Void Residual (PVR)		X					
American Urological Association Symptom Score (AUA-		X					

SS)							
International Consultation on Incontinence Questionnaire - Urinary Incontinence Short Form (ICIQ-UI SF)		X					
Bladder Diary		X					
MRI Safety Screening Questionnaire		X					
Cap Markings			X				
Adverse Event Assessment				X		X	X
MRI (for navigation)				X			
Neuronavigation					X		
rTMS Session (EMG recordings)						X	
MRI (BOLD signal changes)						X	
Acceptability of Intervention Measure Questionnaire (AIM)						X	

*Visits 1 and 2 can be combined.

For Controls: Only Visit 1,2 and 3. No Cap markings, Neuronavigation, rTMS session (Visit 4) or Follow-up Visit 5

Patient's information and study data will be collected on paper or electronic formats and will be recorded and stored in REDCap and excel sheets on the password- controlled computer and network. Data will be recorded as coded with no names but may include some of the 18 identifiers. Patient paper charts will be stored in PI or research Coordinator's office under a locked cabinet at Houston Methodist Hospital, Department of Urology. Electronic data will be stored in REDCap and excel sheet on corporate network on a secure server with access limited to PI and other research directly involved in data collection.

Long Term Follow-Up

As a single-session proof-of-concept study focused on immediate mechanistic signals, there is no long-term clinical follow-up. However, a safety check (phone call) will be conducted **one month** after intervention to ensure no delayed adverse events occurred.

Humanitarian Use Device (HUD)
Not Applicable. The Magstim Rapid2 is not being used under a Humanitarian Device Exemption (HDE) for this protocol. It is being used as an investigational device in a clinical research study.

7.0 Data and Specimen Banking

There will be no bio specimens collected for this study. We will only collect the PVR data, functional MRI data and questionnaires outcomes at baseline and post rTMS treatments. All the other data collected will be standard of care. The data will be collected and recorded using some of the 18 identifiers. The data collected will be stored in REDCap database and excel sheets with access given to the research staff involved directly with this project. The study will be monitored, evaluated and data will be assessed by PI.
The principal investigator or her designee or the investigational site will maintain all the essential study documents and source documentation that support the data collected on the study subjects in compliance with applicable regulatory requirements.

8.0 Sharing of Results with Subjects

Study-Level Results Aggregate results of the research will not be shared with participants immediately upon completion of their individual visits. However, once the full study is completed and the data are analyzed, a summary of the findings regarding the safety and physiological impact of pSMA-targeted rTMS will be made available to participants upon request.

Individual Results and Investigational Data Because the rTMS parameters and the fMRI/EMG measurements are used for investigational and mechanistic purposes, rather than for clinical diagnosis or treatment, individualized results (such as specific cortical activation maps or EMG amplitude readings) will not be routinely shared with the subjects or their primary care physicians. Participants will be informed during the consent process that these procedures are for research purposes and are not intended to guide their personal clinical care.

9.0 Study Timelines

Each subject's active participation will last approximately **6 to 8 weeks (+/- 2 weeks)**. This includes a screening period (Visit 1 and 2) to confirm eligibility and collect baseline metrics, MRI scan (Visit 3) and a single intensive treatment visit (Visit 4) involving neuronavigated rTMS, EMG, and post-stimulation fMRI. Participation ends after a safety follow-up phone call conducted 1 month (Visit 5) after the treatment visit.

Active participation for the control arm will last less than 4-6weeks. This includes the initial screening and baseline questionnaire period (Visits 1 and 2), followed by the single baseline fMRI scan (Visit 3), after which their study participation is complete.
It is anticipated that it will take **12 months** to enroll all 20 subjects. This timeline accounts for the specialized nature of the inclusion criteria, the coordination required between the Urology clinic

and the imaging/neuromodulation facilities, and the thorough screening process required to ensure subject safety for rTMS.

The estimated time to complete this study is **21 months** after the study begins.

10.0 Inclusion and Exclusion Criteria

We plan to recruit 10 adult males (22 - 80 years old) with a history of prostate treatment and who meet the inclusion and exclusion criteria detailed in Table 1 and 10 CC who meet the inclusion and exclusion criteria detailed in Table 2. We selected a time frame of ≥6 months post radical prostatectomy because pelvic floor recovery and neuroplastic rehabilitation are most effective when initiated early, as recommended by the 2024 2024 American Urological Association (AUA)/Society of Genitourinary Reconstructive Surgeons (GURS)/Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (SUFU) Guideline on IPT, yet not so early that they interfere with postoperative healing.[1] Patients will be recruited from our high-volume tertiary urology. Adults with UTI at the time of screening, as seen in Table 1, will be eligible after adequate treatment, and those with recent interventions for OAB will be eligible following washout periods.

Inclusion	Exclusion
• Adult patients (22 to 80 years old) • Males (biological sex at birth) • History of prostate treatment (e.g., prostatectomy, transurethral resection of prostate (TURP), Holmium Laser Enucleation of the Prostate (HoLEP), Aquablation, transurethral water vapor therapy, photoselective vaporization of the prostate, etc) ≥6 months prior • Answer yes to any sub-item of question 6 of the ICIQ-UI SF "When does urine leak?" (e.g., leaks before reaching toilet, cough/sneeze, during sleep, physical activity, post void dribbling, or no obvious reason). • Individuals with Montreal Cognitive Assessment (MoCA) score >10 will be eligible • Is eligible per MRI safety questionnaire form	• Answers never to Question 6 of ICIQ-UI-SF "When does urine leak?" • Contraindications to MRI • Contraindication to rTMS# (personal or immediate family history of seizure disorder, implanted electronic devices or conductive objects in or near the head) • Active UTI (eligible after adequate treatment) • Intradetrusor onabotulinumtoxinA injection within the past 6 months. • Active use of sacral neurostimulator (SNS) or posterior tibial nerve stimulation (TNS). Those with a history of SNS/TNS can participate if their last stimulation was more than 3 months prior to recruitment. • Clinically diagnosed neurological disorders, including Multiple sclerosis, Parkinson's disease, cerebral aneurysm, hydrocephalus, spinal cord injury with motor or sensory deficits, and advanced dementia (advanced cognitive impairment) defined by Montreal cognitive assessment score of ≤10 •Parenchymal brain lesions and hemorrhagic stroke within the last 12 months • Taking any medications such as bupropion or substances (heavy alcohol use) that can lower the seizure threshold • Diagnosis of interstitial cystitis, pelvic radiation, bladder augmentation • Post-void Residual (PVR) > 250cc • Incarcerated patients.

Table 1: Main inclusion and exclusion criteria for IPT cohort
Contraindications listed in the Magstim Rapid2 System operating manual (v2017)

Inclusion	Exclusion
• Adult patients (22 to 80 years old) • Males (biological sex at birth) • History of prostate treatment (e.g., prostatectomy, transurethral resection of prostate (TURP), Holmium Laser Enucleation of the Prostate (HoLEP), Aquablation, transurethral water vapor therapy, photoselective vaporization of the prostate, etc) ≥6 months prior • Selects ONLY "never – urine does not leak" on Question 6 of the ICIQ-UI SF "When does urine leak?" • Total ICIQ-UI SF score = 0 • Individuals with Montreal Cognitive Assessment (MoCA) score >10 will be eligible • Is eligible per MRI safety questionnaire form	• Answer yes to any sub-item of question 6 of the ICIQ-UI SF "When does urine leak?" (e.g., leaks before reaching toilet, cough/sneeze, during sleep, physical activity, post void dribbling, or no obvious reason). • Contraindications to MRI • Active UTI (eligible after adequate treatment) • Intradetrusor onabotulinumtoxinA injection within the past 6 months. • Active use of sacral neurostimulator (SNS) or posterior tibial nerve stimulation (TNS). Those with a history of SNS/TNS can participate if their last stimulation was more than 3 months prior to recruitment. • Clinically diagnosed neurological disorders, including Multiple sclerosis, Parkinson's disease, cerebral aneurysm, hydrocephalus, spinal cord injury with motor or sensory deficits, and advanced dementia (advanced cognitive impairment) defined by Montreal cognitive assessment score of ≤10 • Diagnosis of interstitial cystitis, pelvic radiation, bladder augmentation • Post-void Residual (PVR) > 250cc • Incarcerated patients.

Table 2: Main inclusion and exclusion criteria for Continent Controls

11.0 Vulnerable Populations

This research study does not include individuals who are vulnerable to coercion or undue influence. As defined in the eligibility criteria, the study excludes vulnerable populations, including children, pregnant women, cognitive impairment and prisoners.

12.0 Local Number of Subjects

Number of Subjects Expected to be Enrolled/Screened: We anticipate enrolling 23 subjects. In this protocol, enrollment is defined as the point at which a participant signs the informed consent form and undergoes the initial screening assessments (Visit 1).

Number of Subjects Needed to Complete Research Procedures: The target for evaluable data is 20 subjects who successfully complete both the baseline imaging and the intensive rTMS/EMG/fMRI treatment session. We anticipate a screen failure or technical attrition rate of approximately 17% (3 subjects). This buffer is essential to ensure the study reaches its primary aims with a full dataset.

13.0 Recruitment Methods

The Houston Methodist Urology Clinic is one of the largest clinics in the region with a high-volume center for prostate cancer survivors. They include four fellowship-trained Female Pelvic Medicine and Reconstructive Surgeons urologists and three Uro-oncologists. The primary source of subjects will be adult males who have undergone prostate treatment for prostate cancer or benign prostatic hyperplasia and are currently experiencing persistent urinary incontinence (IPT) as defined by updated 2024 AUA/GURS/SUFU IPT Guidelines.[1] Potential subjects will be recruited during their routine follow-up visits or identified through clinical schedule reviews beginning upon IRB approval. CC will be recruited from urology or primary care clinics at HMH. The PI and/or research coordinator will identify potential patients from the clinics through EPIC electronic medical record. Potential patients' medical records will be pre-screened to confirm eligibility. Confirmed eligible patients will be approached by the research coordinator or PI and invited to participate. During the screening visit, the study will be explained in detail, and participants will be given sufficient time to privately review the Informed Consent Form (ICF), discuss it with family, or seek a second opinion. If they choose to participate, they will sign the ICF to be enrolled. An IRB approved flyer will be posted in urology clinic exam rooms.

To compensate participants for their time, they will receive $200 for completing Visits 3 and 4 (up to $400 total). Partial compensation will be provided if they complete Visit 3. They will receive a parking voucher for parking at each visit (up to 4 visits). Compensation will be given to you in the form of a stipend card. It may take up to 3 to 6 weeks to receive compensation in this study.

14.0 Withdrawal of Subjects

(a) Involuntary Withdrawal:
Subjects may be involuntarily withdrawn from the study if Principal Investigator determines it is in the subject's best interest. They can be removed from the study if:
• They become ineligible to participate.
• They do not follow instructions from research.
• If their condition changes and they need other treatment that is not allowed while they are part of the study
• The study is suspended or cancelled.
If the subject is withdrawn at the researcher's discretion, the reason for withdrawal must be documented in the subject's source file. If they are taken out of active participation, ongoing follow up may continue.

(b) Voluntary Withdrawal:
If a subject wants to withdraw from the study, they should specify the reason in writing. They can also revoke their authorization to use or disclose their research data however the data that has been already collected in the study record may continue to be used. Subject can also be partially withdrawn if they decline procedures such as postintervention fMRI (baseline fMRI is compulsory to be enrolled in the study), the follow-up data collection can still be continued until 3 months follow up after the last intervention visit. After a subject completely withdraws from the study, additional data or follow up may not be collected. Data collected up to this point may be used for study data analysis.

15.0 Risks to Subjects

Risk with Functional MRI:
Anything that is metal in the body can heat up or move during fMRI. Patients will be asked at the time of screening to complete MRI screening questionnaires to confirm if they are eligible for MRI. Participants will be asked to remove their eye makeup as some makeup may contain metallic particles. Some patients report being claustrophobic in the scanner, if they experience such

symptoms during the scan, they will be removed from the scanner immediately and will be withdrawn from the study. There are no injections or intravenous (IV) access sites in this study.

For this study, patients will be scanned on either 3T or 7T MRI scanner depending on their medical history and safety requirement for potential body implants that could be contradictory to the Ultra-high field MRI (7T). Both scanners are stronger than other MRI scanners used in hospital to scan brains. The 3T scanner means that it uses 3 tesla magnetic field and 7 T scanner means that it uses 7 tesla magnetic field. Generally, in hospitals, the 1.5 T scanners with 1.5 tesla magnetic field is used. Although, 3T is stronger than 1.5 T, 7T is the strongest of all and has more strict eligibility requirements. Even though there are no known permanent effects on a patient's health with short term exposure in this scanner, some rare risks may include: vertigo, dizziness, metallic taste and headache. Again, the effects are rare and temporary. Patients will be removed from the scanner immediately if they experience any unusual sensation or discomfort.

Risk with Neural navigator and rTMS:
Like any intervention, there are associated risks with the use of neuronavigated rTMS. The most common being headaches, mild scalp discomfort or irritation, and neck pain. Additionally, in extremely rare cases, fainting, seizures, hearing, and psychiatric disturbances have been reported in some individuals. The rTMS device and the treatment sessions may involve risks to subjects (or the embryo or fetus; if the subject is or may become pregnant) which are currently unforeseeable.

As with any research study, there may be additional risks that are unknown or unexpected. If these become known, the study team will notify the IRB with the modification and the subject in a timely manner of any changes that may change subject's willingness to participate. If new information is provided during the active study; subjects will be re- consented to confirm their willingness to continue the study.

CC are exposed to **MRI risks only** (3T/7T; claustrophobia, implant heating, vertigo/metallic taste).

16.0 Potential Benefits to Subjects

Incontinence after prostate treatment (IPT) significantly diminishes quality of life and carries a high economic and emotional burden. While prevalent, current surgical and behavioral therapies offer limited success for many men. This proof-of-concept study is the first to evaluate whether non-invasive brain neuromodulation via rTMS can improve pelvic floor control by targeting the pelvic supplementary motor area (pSMA).
While there may be no direct clinical benefit to current participants, this research aims to spark a paradigm shift from traditional "sphincter-centric" treatments to a "cerebral control" model. The results will significantly impact the field by:

- **Advancing Mechanistic Understanding:** Identifying how modulating the pSMA can restore the brain-bladder networks necessary for urinary control.
- **Establishing Feasibility:** Evaluating rTMS as a viable, non-invasive alternative to invasive surgical implants like artificial sphincters or male slings.

There is **no direct clinical benefit** to the subjects from taking part in this research. The primary purpose of this study is to gather safety and mechanistic data. **The magnitude of any physiological change induced by a single rTMS session is expected to be temporary, and the duration of any potential change in muscle tone is likely limited to the time immediately following the stimulation session. Participants are informed during the**

consent process that they should not expect an improvement in their urinary symptoms as a result of participating in this study.

17.0 Data Management and Confidentiality

Statistical and Data Analysis Plan

For primary outcomes (Aim 1), feasibility and acceptability will be summarized using descriptive statistics. Continuous variables will be reported as means with standard deviations when normally distributed, or as medians with interquartile ranges when non-normality is observed. Categorical variables will be summarized as counts and percentages with corresponding 95% confidence intervals. Feasibility will be assessed by calculating recruitment and retention rates and the corresponding 95% confidence intervals. Satisfaction will be evaluated by the proportion of participants endorsing positive ratings; if ≥80% of participants report satisfaction, the program will be considered to have high acceptability. Safety outcomes will be summarized descriptively by frequency and type of adverse events, with exact 95% confidence intervals for proportions.

For secondary outcomes (Aim 2), structural and functional MRI data will be pre-processed in FSL software. Group analyses will be conducted by transforming data into Talairach space, with significant voxels identified via Student's t-test. Baseline and post-treatment rTMS scans will be compared for each group by examining BOLD signals from patient fMRI scans to assess changes in SMA activity. Pelvic floor EMG signals will be recorded during rTMS sessions and processed in MATLAB using standardized detrending, denoising, and bandpass filtering procedures. The amplitude of each EMG signal during the first three and last three pulse trains and the average change from baseline will be computed. Pre- to post-treatment changes in EMG amplitude will be compared within subjects and between stimulation conditions (HF vs. LF) to determine frequency-specific effects on PFM tone. Comparison of baseline pSMA BOLD between IPT and CC will be made. Between-group comparison of pSMA functional connectivity during natural bladder filling will be made between CC and subjects with IPT. As this is an exploratory, proof-of-concept pilot study, these comparative neuroimaging analyses are hypothesis-generating and do not affect the primary statistical power of the interventional trial.

Data collected for the research purpose is considered subject's personal data and will be protected as per Houston Methodist policies for Protected Health Information. Data collection parameters have been carefully considered and have been limited to the most important information required for the purpose of this study. This includes the subject's medical history, diagnoses, tests results, treatments, progress notes and summaries. This information is required to confirm a patient's eligibility to participate in this study. Patient's information and study data will be collected on paper charts and will be recorded and stored in REDCap and excel sheets on the password-controlled computer and network. Data will be recorded as coded with no names but may include some of the 18 identifiers. Patient paper charts will be stored in PI or research Coordinator's office under a locked cabinet at Houston Methodist Hospital, Department of Urology. Electronic data will be stored in REDCap and excel sheets on corporate network on a secure server with access limited to PI and other research directly involved in data collection.

All research staff members involved in the collection and handling of patient's data will have proper training about maintaining patients' data privacy and confidentiality. Data safety monitoring will be routinely performed during the study to assess compliance with the study protocol and institutional and other applicable guidelines. PI will be responsible for verifying the transparency of the data collected with adequacy and accuracy. The study data will be stored in locked cabinets for at least 6 years after the study completion.

Personal data collected may be released to the study funding agency, Houston Methodist Hospital, the institutional Review Board, the United States Food and Drug Administration and its representatives and other government agencies if needed.

Although in most cases, the information released to some of these entities/agencies may contain codified patient's information, IRB, FDA, or other government agencies may review records containing personal information for the sake of verifying the credibility and authenticity of the data collected.

Identifier (or parts of)	Recorded	Disclosed	Comment
Names	Yes	Yes	If required by the IRB and FDA to verify the data authenticity
All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and elements of dates (including year) indicative of such age	Yes	Yes	If required by the IRB and FDA to verify the data authenticity
Phone numbers; Fax numbers	Yes	Yes	Not Applicable
Email address	Yes	Yes	Not Applicable

18.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

Safety Plan:

All members of the study team will stay current with training in the protection of human research participants and HIPAA. We will obtain Institutional Research Board (IRB) approval for this study by Houston Methodist Research Institute (HMRI) (in progress). The PI will regularly monitor the data in collaboration with the research team, with periodic review by HMRI IRB as outlined in the Protection against Risk section. Further, we will minimize risks by using rigorous data security protocols to protect subject confidentiality and comply with all federal and HIPAA requirements. The study team will identify protocol deviations (e.g., violation of human subject confidentiality or comprised data integrity) and will ensure expedient reporting to the IRB.

Data Safety Monitoring Committee (DSMC): This study will utilize the HMRI Data Review Committee (DRC) as a resource for data and safety monitoring. Safety oversight will be under the direction of the Data Safety Monitoring Committee. This committee will consist of an specialists in the Departments of Urology and psychiatry who will be familiar with IPT and neuromodulation. The members of this committee will not be directly involved in the conduct of the study.
Measures will be taken to minimize any perceived conflict of interest. The committee members will have adequate knowledge about the project and will perform a regular review of study data to evaluate patient safety, privacy, confidentiality, and efficacy of the treatments bi-annually.

- Prior to initiating patient enrollment, the committee will meet to discuss the process of conducting biannual meetings and to create a data safety monitoring plan which will include each data element to be evaluated.
- At the end of each annual meeting, the committee will provide detailed feedback and recommendations in a written report.
- Clinical safety data including the following will be evaluated:
    - Overall protocol accrual and expected number of individuals recruited.
    - Individual registrations and eligibility.

o All adverse events (AEs) occurring from time of informed consent through final study visit will be captured and recorded. All AE, serious AE, unanticipated adverse device effects (UADEs) will be tracked on a **"Site AE log**" for all subjects in this study.
o Response evaluations.
o Whether protocol-specific rules are being followed.
o Study amendments/modifications that may have occurred since the last review.

Hard stops for individual participants: Participants will fill out a set of questionnaires before and after each treatment session to identify any potential complication related to rTMS. rTMS has extensively and safely been used in many lower urinary tract symptom trials[27].
Neuronavigation system is also FDA cleared and is commonly used in combination with TMS for tumor mapping in neurosurgical pre-planning[28-30]. If a participant experiences a discomfort with any of the planned interventions (fMRI, Neuronavigation, rTMS), these symptoms will be promptly assessed and addressed by repositioning the stimulating coil center within the region of interest and delivering single pulses while soliciting feedback from the participants regarding any pain or discomfort they may be experiencing. This will be discussed with our safety monitoring team and IRB and we will proceed according to their recommendation. Individual AEs will be tracked on a "**Subject AE tracking log**."

Hard stops specifics: The rTMS treatment rooms are located within our clinic which is in a hospital setting, making speedy treatment in case of an adverse reaction feasible. Having a history of seizures are within the exclusion criteria for our study. However, our team is familiar with recognizing both events and will respond accordingly. In the rare event that a seizure occurs (the possibility of occurrence even individuals with history of seizure is <1.0 %) stimulation will be terminated, and appropriate clinical care provided Additionally, the participant will be withheld from continuing with the study (hard stop) if either of these events take place.

Safety monitoring committee will meet bi-annually and review the reports of any discomfort or side effects. The study will be stopped at any point that the IRB or safety monitoring committee makes that recommendation. We will comply with the following requirements:

a. Any unanticipated adverse effects will be investigated immediately and if unreasonable risk to the patient is possible, the study will be terminated, and all regulating authorities and participating investigators will be notified. Termination shall occur not later than 5 working days after the sponsor makes this determination and not later than 15 working days after the sponsor first received notice of the effect (21 CFR 812.46(b)(1&2)).

b. A terminated investigation may not be resumed without IRB and FDA approval (21 CFR 812.46(c)).

ClinicalTrials.gov Requirements
This study will comply with the current regulations for registration and results reporting in ClinicalTrials.gov and will be registered.

19.0 Provisions to Protect the Privacy Interests of Subjects

Data collected for the research purpose is considered subject's personal data and will be protected as per Houston Methodist policies for Protected Health Information. Data collection parameters have been carefully considered and has been limited to the most important information required for the purpose of this study. To protect patient's privacy, only study PI, sub-

I and research coordinator will be directly involved in data collection process and the study visits will be performed in a private clinic room. The purpose of the personal data collection will be carefully defined in the informed consent form. PI will take all the steps to ensure that patient's personal data is not disclosed, copied, or altered for any purpose other than defined in informed consent form. Patients will have the right to deny participating and withdraw at any time.

20.0 Compensation for Research-Related Injury

In the event of a research related injury, necessary medical treatment will be available. Cost of medical treatment will be billed to the patient or their insurance provider. There are no plans to provide financial compensation.

Consent Form

If you have a research-related injury, Houston Methodist providers will provide medical care. A research-related injury is an illness directly caused by the study device or a study procedure. A research-related injury does not include:

- injuries directly caused by the natural worsening (progression) of an underlying disease or medical condition, or
- injuries caused by you not following the instructions in this consent form.

However, this medical care will be billed to you and/or your insurance provider in an ordinary manner. You will not be reimbursed for expenses or compensated financially by Houston Methodist or the NIH for medical expenses for a research-related injury or for other expenses such as lost wages, disability, or discomfort. However, by signing this form you are not giving up any of your legal rights.
You and/or your health care plan may be financially responsible for the cost of care and treatment of any complications resulting from the research tests, procedures, and/or drugs.
If you think you have a research-related injury or have questions about a research- related injury, you should contact the study doctor or call the Houston Methodist IRB at 346-356-1400.

21.0 Economic Burden to Subjects

There are no direct costs to the subjects for participation in this research study. All study-related procedures, including the **neuronavigated rTMS** sessions, **fMRI scans**, and **pelvic floor EMG** assessments, are provided at no cost to the participant and are funded by the research department.

However, participants may be responsible for the following indirect "out-of-pocket" expenses:

- **Travel and Parking:** Costs associated with traveling to the Houston Methodist Hospital and parking fees.
- **Time Commitment:** The opportunity cost associated with the duration of the visits (approximately 1 hour for the screening visit and up to 2 hours for the treatment session).

To mitigate these economic burdens, a total compensation of **$400** is provided for Visit 3 and 4 upon completion of the study milestones to help offset the costs of parking, fuel, and travel. Parking vouchers will also be provided.

Participants in the CC cohort will receive $200 total upon completion of Visit 3.

22.0 Consent Process

An Informed consent form is required for each subject. The PI, sub-I and/or research coordinator will be involved in completing the informed consent process. The consent process will take place at the Houston Methodist Urology Clinics. The physician will have assessed the competence of the subject to consent. The investigator will tell the patient the basics of the study and determine whether they might be interested. The coordinator will then go over the study and consent form with the patient to make sure they understand everything and have plenty of time to ask questions. The Principal Investigator is responsible for ensuring that Informed consent form is obtained prior to any study related procedures and data collection.

The Informed Consent form will be approved by the IRB prior to implementation. If new information becomes available during the study that can significantly affect a subject's future health and medical care, that information will be provided via a revised informed consent form. The consent modification(s) will also require IRB approval and the subject will sign the revised ICF once it is approved by the IRB.

The Informed Consent can be provided via paper form or electronic form in REDCap. This study will have the option for the entire consent process to occur by in person or by telephone review of the ICF with the appropriate research team members. The electronic signature may be provided following telephone or in person review.

23.0 Process to Document Consent in Writing

The study will follow **HRP-091 - SOP - Written Documentation of Consent**. Informed consent will be obtained from all participants before any study-specific procedures are performed. The process will be conducted in a private setting (such as a clinic exam room) to ensure confidentiality. The Principal Investigator or a trained research coordinator will explain the study's purpose, procedures, risks, and benefits. Participants will be given ample time to read the **Informed Consent Form (ICF)**, ask questions, and discuss participation with family or primary physicians.

Written documentation of consent is required and **will not be waived**. The signature of the subject and the individual obtaining consent will be captured on the IRB-approved ICF.

24.0 Setting

The research will be conducted entirely within the Houston Methodist. Potential subjects will be identified and recruited at the Houston Methodist Urology Clinic. The clinic will provide the necessary patient volume of post-prostatectomy men experiencing stress urinary incontinence. Review of Electronic Medical Records (EMR) and initial screening discussions will occur within these clinical spaces. All research activities are conducted internally at Houston Methodist (fMRI will be conducted at Houston Methodist Translational Imaging Center and rTMS will be performed at the Houston Methodist Neuromodulation Laboratory).

25.0 Resources Available

The study will be conducted at **Houston Methodist**, utilizing the high-volume **Urology Clinic** which treats over 100 men annually with post-prostatectomy incontinence. To reach our target of **23 subjects**, we only need to recruit approximately **20% of this eligible population**, making

the 12-month recruitment timeline highly feasible. The PI will dedicate 10% effort to oversight, supported by a fellow and research coordinator at 50% effort.

Research procedures will utilize the **Translational Imaging Center (TIC)** for 3T and 7T fMRI and the **Neuromodulation Laboratory** for neuronavigated rTMS and concurrent pelvic floor EMG. Because these facilities are located within a tertiary hospital, subjects have immediate access to emergency medical services.

To ensure protocol adherence, all staff must complete CITI training and attend a mandatory initiation meeting to review duties, safety protocols, and the specific rTMS/fMRI sequences. Regular weekly meetings will be held to monitor data quality and subject safety throughout the study duration.

26.0 Multi-Site Research

This is a single site study. All the research activities will be performed at Houston Methodist Hospital, Department of Urology.
Disclosure: As per FDA requirement (21 CFR 812),

a. The investigator agrees to the commitment of:
    i. conducting the investigation in accordance with the agreement, the investigational plan, Part 812 and other applicable FDA regulations, and conditions of approval imposed by the reviewing IRB and FDA (per 21 CFR 812.100)
    ii. supervising all testing of the device involving human subjects (per 21 CFR 812.110(c)); and
    iii. ensuring that the requirements for obtaining informed consent are met

b. Investigator will provide certification that all participating investigator(s) have signed the agreement and that no investigator will be added until the agreement is signed

c. Investigator will provide sufficient and accurate financial disclosure information and update information if any relevant changes occur during the investigation and for one year following the completion of the study (per 21 CFR 812.110(d));

d. Investigator will ensure to inform FDA if the investigator was involved in an investigation or other research that was terminated, an explanation of the circumstances that led to termination

[i] This template satisfies AAHRPP elements 1.7.B, I.8.B, I-9, II.2. A, II.2.I, II.3.A, II.3.B, II.3.C-II.3.C.1, II.3.D-F, II.4.A, III.1.C-F, II.2.D

References

1. Breyer BN, Kim SK, Kirkby E, Marianes A, Vanni AJ, Westney OL. Updates to Incontinence After Prostate Treatment: AUA/GURS/SUFU Guideline (2024). J Urol. Published online July 27, 2024. doi:10.1097/JU.0000000000004088
2. Penson DF, Barocas DA; the Comparative Effectiveness Analysis of Surgery and Radiation (CEASAR). Comparing the Effects of Surgery, Radiation Therapy, and Active Surveillance on Men With Localized Prostate Cancer—The CEASAR Study [Internet]. Washington (DC): Patient-Centered Outcomes Research Institute (PCORI); 2020 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK604722/ doi: 10.25302/1.2020.CE.12114667
3. Hoyland K, Vasdev N, Abrof A, Boustead G. Post-radical prostatectomy incontinence: etiology and prevention. Rev Urol. 2014;16(4):181-8. PMID: 25548545; PMCID: PMC4274175.
4. Ratcliff CG, Cohen L, Pettaway CA, Parker PA. Treatment regret and quality of life following radical prostatectomy. Support Care Cancer. 2013 Dec;21(12):3337-43. doi: 10.1007/s00520-013-1906-4. Epub 2013 Aug 2. PMID: 23907238; PMCID: PMC3823814.
5. Griffiths D. Neural control of micturition in humans: a working model. Nature reviews Urology. 2015;12(12):695-705
6. Khavari R, Chen J, Boone T, Karmonik C. Brain activation patterns of female multiple sclerosis patients
with voiding dysfunction. Neurourology and urodynamics. 2020;39(1)/
7. Yani MS, Fenske SJ, Rodriguez LV, Kutch JJ. Motor cortical neuromodulation of pelvic floor muscle tone: Potential implications for the treatment of urologic conditions. Neurourol Urodyn. 2019 Aug;38(6):1517-1523. doi: 10.1002/nau.24014. Epub 2019 May 1. PMID: 31044482; PMCID: PMC6660362.
8. Kairys AE, Schmidt-Wilcke T, Puiu T, et al. Increased brain gray matter in the primary somatosensory cortex is associated with increased pain and mood disturbance in patients with interstitial cystitis/painful bladder syndrome. The Journal of urology. 2015;193(1):131–137.
9. Kutch JJ, Yani MS, Asavasopon S, et al. Altered resting state neuromotor connectivity in men with chronic prostatitis/chronic pelvic pain syndrome: A MAPP: Research Network Neuroimaging Study. NeuroImage: Clinical. 2015;8:493–502.
10. Kilpatrick LA, Kutch JJ, Tillisch K, et al. Alterations in resting state oscillations and connectivity in sensory and motor networks in women with interstitial cystitis/painful bladder syndrome. The Journal of urology. 2014;192(3):947–955.
11. Parekh AR, Feng MI, Kirages D, Bremner H, Kaswick J, Aboseif S. The role of pelvic floor exercises on post-prostatectomy incontinence. J Urol. 2003 Jul;170(1):130-3. doi: 10.1097/01.ju.0000072900.82131.6f. PMID: 12796664.
12. Inouye BM, Premo HA, Weil D, Peterson AC. The male sling for stress urinary incontinence: tips and tricks for success. Int Braz J Urol. 2021 Nov-Dec;47(6):1131-

1135. doi: 10.1590/S1677-5538.IBJU.2020.1122. PMID: 33861057; PMCID: PMC8486443.
13. Litwiller SE, Kim KB, Fone PD et al: Post-prostatectomy incontinence and the artificial urinary sphincter: A long-term study of patient satisfaction and criteria for success. J Urol 1996; **156:** 1975
14. Averbeck MA, de Almeida SHM. Surgical strategies in artificial urinary sphincter revision surgery: troubleshooting the complications. Transl Androl Urol. 2024 Aug 31;13(8):1641-1649. doi: 10.21037/tau-22-830. Epub 2024 Aug 16. PMID: 39280650; PMCID: PMC11399024.
15. Fregni F, Pascual-Leone A. Technology insight: noninvasive brain stimulation in neurology-perspectives on the therapeutic potential of rTMS and tDCS. Nat Clin Pract Neurol. 2007;3(7):383–93. https://doi.org/10. 1038/ncpneuro0530.
16. Janicak PG, Dokucu ME. Transcranial magnetic stimulation for the treatment of major depression. Neuropsychiatr Dis Treat. 2015;11:1549–60. https://doi.org/10.2147/NDT.S67477.
17. Martin JL, Barbanoj MJ, Perez V, Sacristan M. Transcranial magnetic stimulation for the treatment of obsessive-compulsive disorder. Cochrane Database Syst Rev.
18. Griffiths D, Derbyshire S, Stenger A, Resnick N. Brain control of normal and overactive bladder. J Urol. 2005;174(5):1862-1867. doi:10.1097/01.ju.0000177450.34451.97
19. Aloizou AM, Pateraki G, Anargyros K, et al. Transcranial magnetic stimulation (TMS) and repetitive TMS in multiple sclerosis. Rev Neurosci. 2021;32(7):723-736. doi:10.1515/revneuro-2020-0140
20. Salazar BH, Hoffman KA, Lincoln JA, Karmonik C, Rajab H, Helekar SA, Khavari R. Evaluating noninvasive brain stimulation to treat overactive bladder in individuals with multiple sclerosis: a randomized controlled trial protocol. BMC Urol. 2024 Jan 25;24(1):20.
21. Mumford JA, Nichols TE. Power calculation for group fMRI studies accounting for arbitrary design and temporal autocorrelation. Neuroimage. 2008 Jan 1;39(1):261-8. doi: 10.1016/j.neuroimage.2007.07.061. Epub 2007 Aug 19. PMID: 17919925; PMCID: PMC2423281.
22. Rahnama'i MS. Neuromodulation for functional bladder disorders in patients with multiple sclerosis.
Multiple sclerosis. 2020;26(11):1274-1280
23. Noh TS, Rah YC, Kyong JS, et al. Comparison of treatment outcomes between 10 and 20 EEG electrode location system-guided and neuronavigation-guided repetitive transcranial magnetic stimulation in chronic tinnitus patients and target localization in the Asian brain. Acta Otolaryngol. 2017;137(9):945–51. https://doi.org/10.1080/00016489.2017. 1316870.
24. Sparing R, Hesse MD, Fink GR. Neuronavigation for transcranial magnetic stimulation (TMS): where we are and where we are going. Cortex. 2010;46(1):118–20. https://doi.org/10.1016/j.cortex.2009.02.018.
25. Khavari R, Tran K, Helekar SA, Shi Z, Karmonik C, Rajab H, John B, Jalali A, Boone T. Noninvasive, Individualized Cortical Modulation Using Transcranial Rotating Permanent Magnet Stimulator for Voiding Dysfunction in Women with Multiple Sclerosis: A Pilot

Trial. J Urol. 2022 Mar;207(3):657-668. doi: 10.1097/JU.0000000000002297. Epub 2021 Oct 25. PMID: 34694911; PMCID: PMC9724016.
26. Colbert KL, Salazar B, Sharma K, Khavari R, High R. PD31-09 Effects of repetitive transcranial magnetic stimulation of the supplementary motor area and dorsolateral prefrontal cortex on pelvic floor muscle activity in patients with overactive bladder. Journal of Urology. 2025 May 1;213(5S):e1143. https://doi.org/10.1097/01.JU.0001110120.10144.d3.09
27. Nardone R, Versace V, Sebastianelli L, et al. Transcranial magnetic stimulation and bladder function: A systematic review. *Clin Neurophysiol*. 2019;130(11):2032-2037. doi:https://doi.org/10.1016/j.clinph.2019.08.020
28. Verification of a 10-20 Targeting Protocol Used During Transcranial Magnetic Stimulation Sessions for Tinnitus. *Brain Topogr*. 2018;31(4):690-699. doi:10.1007/s10548-018-0636-9
29. Herwig U, Satrapi P, Schönfeldt-Lecuona C. Using the international 10-20 EEG system for positioning of transcranial magnetic stimulation. *Brain Topogr*. 2003;16(2):95-99. doi:10.1023/b:brat.0000006333.93597.9d
30. De Witte S, Klooster D, Dedoncker J, Duprat R, Remue J, Baeken C. Left prefrontal neuronavigated electrode localization in tDCS: 10-20 EEG system versus MRI-guided neuronavigation. *Psychiatry Res Neuroimaging*. 2018;274:1-6. doi:10.1016/j.pscychresns.2018.02.001