University of Pittsburgh | Institutional Review Board
Office of Research Protections

# STUDY CLOSURE

| | |
|---|---|
| Date: | May 20, 2025 |
| IRB: | MOD22030048-007 |
| PI: | Christopher Chermansky |
| Title: | Phenotyping Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS) by ICE-MRI Based Bladder Permeability Assay |
| Funding: | Name: National Institute of Diabetes and Digestive and Kidney Diseases , Grant Office ID: FP00022828, Funding Source ID: DK108397 |
| IRB Coordinator: | Cheryl Moore |

The Institutional Review Board acknowledges your request for closure of the above referenced protocol effective as of 5/20/2025. As part of this action:

- The protocol is permanently closed to enrollment.
- All subjects have completed all protocol-related interventions.
- Collection of private identifiable information is completed.
- Analysis of private identifiable information is completed.

**It is the responsibility of Principal Investigator to notify all members of the research team of this action.**

If you have any questions, please contact the University of Pittsburgh Human Research Protection Director, Jean Barone, at (412) 383-1480 or email baronej2@pitt.edu.

*Please take a moment to complete our Satisfaction Survey as we appreciate your feedback.*

# Basic Study Information

1. * **Title of study:**
   Phenotyping Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS) by ICE-MRI Based Bladder Permeability Assay

2. * **Short title:**
   MRI for IC/BPS Patients

3. * **Brief description:**
   We intend to translate a radiation-free, minimally invasive assay of bladder mucosal permeability from preclinical studies (PMC7509285; PMC6028942; PMC8484474) to the clinic. The proposed study will demonstrate the validity of intravesical contrast enhanced magnetic resonance imaging (ICE-MRI) to measure the permeability of human bladder wall in various subtypes of IC/BPS. A key feature of our ICE-MRI assay of bladder permeability is the transurethral catheter instillation of Gadobutrol and Ferumoxytol mixture. After this is placed, subsequent MRI capitalizes on the linear relationship between the concentration of instilled Gadobutrol diffusing passively into the mucosa to cause concentration-dependent changes in T1 relaxation rate (1/T1 relaxation time) of the mucosa. While Gadobutrol instilled into bladder lumen diffuses into mucosa down the concentration gradient, our preliminary data demonstrate that Hunners lesion accelerates the Gadobutrol diffusion relative to normal areas. The proposed study will generate clinical evidence

for demonstrating that ICE-MRI can be a diagnostic test for bladder-centric phenotype in IC/BPS patients to
complement conventional cystoscopy-based diagnosis. IC/BPS is classified into either hypersensitive bladder with no identifiable pathology explaining the symptoms of IC/BPS, IC/BPS with Hunner lesion (HIC) or IC/BPS with no lesions on cystoscopy (NHIC).
We will test the hypothesis that bladder mucosal permeability of instilled Gadobutrol mixture descends quantitatively from HIC >NHIC >asymptomatic control subjects

4. * **What kind of study is this?**
Single-site study

5. * **Will an external IRB act as the IRB of record for this study?**
○ Yes ● **No**

6. * **Local principal investigator:**
Christopher Chermansky
* **Is this your first submission, as PI, to the Pitt IRB?**
○ Yes ● **No**

7. * **Does the local principal investigator have a financial interest related to this research?**
○ Yes ● **No**

8. **Attach the protocol:**
- Sponsor/Multicenter/Investigator-initiated protocol
- Coordinating Center supplement

- Emergency Use Consent/ Protocol/ FDA Form 3926
- Exempt Application form

Document Category Date Modified Document History

There are no items to display

# Funding Sources

**1. * Indicate all sources of support:**

External funding

**2. * Identify each organization supplying funding for the study:**

| Funding Source | Sponsor's Funding ID | Grants Office ID | Attachments | Pitt Awardee | Grant Recipient |
|---|---|---|---|---|---|
| National Institute of Diabetes and Digestive and Kidney Diseases | DK108397 | FP00022828 | complete grant | no | Lipella Pharmaceuticals |

# Study Team Members

1. * **Identify each person involved in the design, conduct, or reporting of the research:**

| Name | Roles | Department/School | Affiliation | Involved in Consent | Qualifications | Financial Interest |
|---|---|---|---|---|---|---|
| Christopher Chermansky | Principal Investigator | U of Pgh \| School of Medicine \| Urology | Pitt faculty | yes | Dr. Chermansky's role in the grant will be in the direction and supervision of this clinical trial for developing objective diagnosis and treatment m... view all | no |
| Balasubramani Goundappa | Statistician | U of Pgh \| Graduate School of Public Health \| Epidemiology | Pitt faculty | no | Dr. Goundappa is the expert in the area of statistical methodologies for clinical trials and have extensive experience in the analysis of large clin... view all | no |

| Name | Roles | Department/School | Affiliation | Involved in Consent | Qualifications | Financial Interest |
|---|---|---|---|---|---|---|
| Laurie Hope | Secondary Study Coordinator | U of Pgh \| School of Medicine \| Medicine | Pitt staff | yes | Laurie Hope RN will is a urology research RN who will serve as secondary study coordinator to help as needed with study procedures. | no |
| Chan-Hong Moon | Co-investigator | U of Pgh \| School of Medicine \| Radiology | Pitt faculty | no | Dr. Moon's role in the grant will be the direction of MRI imaging at 3.0T clinical scanner, including the use of 3D FLASH and designing the pulse seq... view all | no |
| Vickie Polanco-Garcia | Primary Study Coordinator | U of Pgh \| School of Medicine \| Urology | Pitt staff | yes | Vickie Polanco-Garcia will be the primary research coordinator for this study | no |

| Name | Roles | Department/School | Affiliation | Involved in Consent | Qualifications | Financial Interest |
|---|---|---|---|---|---|---|
| Biatta Sholosh | Co-investigator | U of Pgh \| School of Medicine \| Radiology | Pitt faculty | no | Dr. Shlosh is the radiologist responsible for supervising and interpreting the MR images of patients without prior knowledge of their cystoscopic dia... view all | no |
| Pradeep Tyagi | Co-investigator | U of Pgh \| School of Medicine \| Urology | Pitt faculty | no | Dr. Tyagi's role will be in the translation of ICE-MRI from rodents to humans and interpret the evidence for the feasibility and validity of T1 relax... view all | no |

**2. External team member information: (Address all study team members in item 1. above and leave this section blank)**

| Name | Description |
|---|---|
| There are no items to display | |

3. **Have you,** Christopher Chermansky, **verified that all members of the research team have the appropriate expertise, credentials, training, and if applicable, child clearances and/or hospital privileges to perform those research procedures that are their responsibility as outlined in the IRB application?**

* ● **Yes** ○ No

# Study Scope

*Check all that apply*

**1. * Will this study actively recruit any of the following populations?**

- ☐ Adults with impaired decision-making capacity
- ☐ Children (under the applicable law of the jurisdiction in which the research will be conducted (<18 years for PA))
- ☐ Children who are Wards of the State
- ☐ Employees of the University of Pittsburgh/UPMC
- ☐ Medical Students of University of Pittsburgh as primary research group
- ☐ Nursing School Students of University of Pittsburgh as primary research group
- ☐ Students of the University of Pittsburgh
- ☐ Neonates of uncertain viability
- ☐ Non-viable neonates
- ☐ Non-English speakers
- ☐ Nursing home patients in the state of Pennsylvania
- ☐ Pregnant women
- ☐ Prisoners
- ☑ N/A

**2. * Will any Waivers be requested?**

- ☐ Waiver/Alteration of Consent
- ☐ Waiver to Document Consent
- ☐ Waiver/Alteration of HIPAA
- ☐ Exception from consent for emergency research
- ☑ N/A

**3. * Will this study involve any of the following?**

- [x] Specimens
- [ ] Honest Broker to provide data/specimens
- [ ] Return of Results to Subjects or Others
- [ ] Fetal tissue
- [ ] N/A

**4. * Will Protected Health Information be collected?**

- [ ] Pitt medical records
- [x] UPMC medical records
- [ ] Other Institutions' medical records
- [ ] N/A

**5. * Other Requests?**

- [ ] Deception (if not Exempt, also requires Waiver/Alteration of Consent)
- [ ] Emergency Use / Single Patient Expanded Access (using FDA Form 3926)
- [ ] Placebo Arm
- [ ] Withdraw from usual care
- [x] N/A

**6. * Determining Scientific Review:**

Received External funding where scientific merit was established as a condition of funding

**7. * Has this study (or substantially similar study) been previously disapproved by the Pitt IRB or, to your knowledge, by any other IRB?**

○ Yes ● **No**

*Review the HRPO policy, if participating in research at the VA Pittsburgh Healthcare System or using funding from the VA*

8. * **Does the study use an approved drug or biologic, use an unapproved drug or biologic, or use a food or dietary supplement to prevent, diagnose, cure, treat, or mitigate a disease or condition?**

● **Yes** ○ No

9. * **Does the study evaluate the safety or effectiveness of a device (includes in-vitro laboratory assays)?**

○ Yes ● **No**

10. * **Is this application being submitted to convert an approved study from OSIRIS to PittPRO?** (Tip Sheet)

○ Yes ● **No**

11. * **Does your research protocol involve the evaluation or use of procedures that emit ionizing radiation and, after reviewing this** HUSC guidance, **does your research protocol require HUSC review? (If yes, upload the** HUSC form **in the Local Supporting Documents section). If you are unsure of review requirement, select yes.**

○ Yes ● **No**

# Research Sites

1. **Choose all sites that apply:**
   University of Pittsburgh
   UPMC

   *** Select the University of Pittsburgh sites where research will be conducted:**
   Main Campus – Pittsburgh

   **List university owned off-campus research sites if applicable:**

   Oakland

   *** Select the UPMC sites where research will be conducted:**
   Magee Women's Hospital
   Presbyterian

2. **Describe the availability of resources and the adequacy of the facilities to conduct this study:**
   The Department of Urology provides expert diagnosis and care of IC/BPS, including endoscopic and minimally invasive surgery, continent urinary diversion and intravesical therapy. The Department of Urology maintains a robust research program that encompasses both basic and clinical studies. The trial procedures will be conducted in the Department of Urology Clinical Offices located at UPMC Magee Womens Hospital, 300 Halket Street, Suite 2541 Pittsburgh PA 15213—a state-of-the-art, high volume, outpatient clinical facility encompassing approximately 4500 square feet and includes 5 exam rooms, one cystoscopy suite, including cystoscopes (3x) digital fluoroscopy, transrectal ultrasound equipment, video monitors
   2000 square feet with 10 exam rooms and equipment for cystoscopy, fluoroscopy, and renal ultrasonography. Also, the MRIs will be performed at the UPMC Presbyterian Magnetic Resonance Research Center (MRRC). A research coordinator has dedicated, locked office space for trial files and regulatory binders.

Dr Chermansky and his team has previously conducted several clinical trials with the NICHD Pelvic Floor Disorders Network (PFDN). The combined experience and expertise of this collective group of individuals demonstrates our success in, and commitment to, high caliber clinical research.

# Drugs

1. * **List all drugs, biologics, foods, and dietary supplements to be used in the study:**

| | Generic Name | Brand Name | FDA status | Evaluation Increase Risk | Data Reported to FDA | Attachment Name |
|---|---|---|---|---|---|---|
| View | Ferumoxytol | Feraheme | Approved drug or biologic being **evaluated for a new** indication, population, route of administration, or dosage level not specified in the FDA approved labeling | no | no | package insert |
| View | Gadobutrol | Gadavist | Approved drug or biologic being **evaluated for a new** indication, population, route of administration, or dosage level not specified in the FDA | no | no | package insert |

| Generic Name | Brand Name | FDA status | Evaluation Increase Risk | Data Reported to FDA | Attachment Name |
|---|---|---|---|---|---|
| | | approved labeling | | | |

**2. * Will the study be conducted under an investigational new drug application (IND) and/or require review by the Human Use Subcommittee (HUSC) of the University of Pittsburgh Radiation Safety Committee?**

○ Yes ● **No**

**3. Attach files:** (Attach information not related to a specific drug or not already uploaded elsewhere. Attachments may include justification for why an IND is not required, FDA's IND Acknowledgement Letter, or confirmation receipt from submission to FDA.)

| | Document | Category | Date Modified | Document History |
|---|---|---|---|---|
| View | Letter to Pitt IRB for IND Exemption to STUDY22030048.doc(0.02) | Drug Attachment | 7/10/2022 | History |
| View | Study report (abstract) documenting that there is no increased risk to human participants from mixture of two agents upon instillation (0.01) | Drug Attachment | 7/8/2022 | History |
| View | Figure for poster #69 of northeast AUA(0.01) | Drug Attachment | 7/8/2022 | History |
| View | Poster#69 for 74th Annual Meeting of the Northeastern Section of the AUA(0.01) | Drug Attachment | 7/8/2022 | History |

4. * **Describe your plan to store, handle, and administer drugs so that they will be used only on subjects and be used only by authorized investigators:**
We have experience with a separate trial relating to these two contrast agents for safely storing, handling, and administering them so that only enrolled subjects are administered with contrast agents by authorized investigators. Both these contrast agents will be procured by Investigational Drug Services, UPMC Presbyterian Shadyside Hospital. Prior to use, both these contrast agents will be stored at room temperature with temperature logged by an automatic probe. While the consented subject is undergoing pre-instillation scan in MRI, the two contrast agents will be mixed together by the PI in 250mL water immediately before bladder instillation. Then, 50mL of the mixture will be withdrawn from the IV bag using a 60 mL syringe, and the syringe will be connected to the urethral catheter for instillation of these 2 drugs into the subject for a post-instillation MRI.

5. * **Do you plan to utilize the UPMC Investigational Drug Service (IDS) to dispense the drug?**
○ Yes ● **No**

Click **Continue** as this page was intentionally left blank.

# Recruitment Methods

*** Will you be recruiting individuals for participation in this study?**

● **Yes** ○ No

1. *** Describe who will be recruiting individuals for participation for this study:**

   Christopher Chermansky

2. *** Select all methods to be used for recruitment:**

   Directly approaching potential subjects (in-person)
   Pitt+Me

3. *** Provide details on your recruitment methods:**

   Clinical staff will request permission from potential participants (who are not patients of the investigators) for research staff to approach to discuss the research study. Potential study subjects will be recruited from the clinical practice of the University of Pittsburgh Department of Urology. Eligible patients will be approached by study investigators, and each potential subject will be informed of the rationale for the study, the entry requirements, the procedures involved, the exclusion criteria, the reasons for withdrawal, and the potential risks and alternative options. MRI screening form of MRRC will also be used for determining study eligibility.

   • No "cold-calling" will occur. The participants will first read, ask any and all questions, and then sign the consent form. The principal investigator will sign the investigator's certification statement at the time of obtaining consent.

• We do not expect to recruit patients for this trial through referrals from other health care providers; however, if another physician is aware of this trial and would like to refer his/her patient to us, and if the patient expresses interest in the study participation, the other physician will instruct the patient to either contact the research team directly or the patient will provide an IRB approved written authorization to the caregiver to share with the research that he/she is interested in study participation, share with the research the health information related to eligibility for inclusion into the study, and allow the involved researchers to contact the patient for additional discussions related to the study

• We do not anticipate difficulty in recruiting for this study. Dr. Chermansky in the Department of Urology at UPMC has a successful history of recruiting subjects for IC/BPS studies. In addition, the national Interstitial Cystitis Association can be engaged as needed to announce to its 50,000 members this IC/BPS study. As the leading patient advocacy group that speaks with and for patients with IC/BPS, the foundation can be an important asset in helping to make patients and health care providers aware of this study.

The Clinical Research Coordinator (CRC) will screen the subjects further, as per the clinical PI (Dr. Chermansky), to determine if they meet the inclusion/exclusion criteria. Upon activation of the study, the clinical Research Coordinator will be responsible for facilitating the consent process, ascertaining that subjects meet study requirements, and complete and accurate collection and recording of all data elements required by the research study. The clinical Research Coordinator assists the PI in screening patients and improving accrual. The Research Coordinator will provide subjects with protocol calendars, assures compliance with clinical research study requirements, and facilitate study-specific orders and radiology review.

University Pittsburgh Medical center (UPMC) is a large network hospital and we

have access to patients coming to urology and urogynecology clinics for this study. Dr. Chermansky has a strong history of successful recruitment for IC/BPS clinical trials. Dr. Chermansky has worked with Dr. Chancellor, Chief Medical Officer at Lipella Pharmaceuticals, for approximately 20 years, and this relationship will allow seamless collaboration between this university clinical trial site and Lipella to ensure safe and ethical clinical trial study. Dr. Chermansky routinely treats 12-15 IC/BPS patients each month. Pitt's Clinical and Translational Science Institute also has a centralized participant recruitment program called
Pitt+Me®. It is a voluntary database of individuals willing to consider participation in research studies. To enhance participation in clinical trials, information regarding the trial will be available to the extended University of Pittsburgh Community and referring physician network through
registration in the Pitt+Me research platform. Pitt+Me® pre-screens the participants for basic inclusion criteria and has been proven extensively successful for recruitment. In addition to patients seen within the Department of Urology, Dr Chermansky collaborates closely with his urogynecology colleagues within the Women's Center for Bladder and Pelvic Health at UPMC Magee Womens Hospital (MWH) and its 7
satellite offices. The proximity of our clinical offices at MWH enables our research staff to efficiently enroll women seeking care for Pelvic Floor disorders. Our integrated EMR (Epic Care) has been customized to include validated condition specific measures of pelvic symptoms and
staff can remotely screen charts for study eligibility from multiple locations.

**4. * Describe all compensation/incentives offered to participants and timing of these offers:**

Each consented participant will receive free parking for all study visits. Each subject will receive a payment of $50 upon completing screening and cystoscopy. Then,

each subject will receive $250 upon completion of both MRIs. Thus, for complete participation in the study, each participant will receive a total of $300.

5. **Recruitment materials:** (attach all material to be seen or heard by subjects, including advertisements and scripts)

| Document | Category | Date Modified | Document History |
| --- | --- | --- | --- |
| There are no items to display | | | |

# Study Aims

1. * **Describe the purpose, specific aims, or objectives and state the hypotheses to be tested:**

Recently, the chronic pelvic pain working group classified IC/BPS into either hypersensitive bladder with no identifiable pathology explaining the symptoms of IC/BPS, IC/BPS with Hunner lesion (HIC) or IC/BPS with no lesions on cystoscopy (NHIC). Although the etiology of IC/BPS is multifactorial, a large body of evidence supports the impairment of bladder mucosal permeability as a major pathophysiological cause in HIC. Yet, there remains variability (5-57%) in the true identification of IC/BPS that is bladder-centric on the basis on cystoscopy. Therefore, a minimally invasive, assay that reliably measures bladder permeability without evoking pain or exposing ionizing radiation to subjects may be able to meet the FDA regulatory criteria for a diagnostic test. Such a test could objectively phenotype IC/BPS that is bladder-centric, thereby identifying patients who would be most likely to benefit from anti-inflammatory therapies. A radiation-free, objective diagnostic test of bladder permeability could also enable the objective selection of IC/BPS patients for clinical trials of newer therapies that target bladder pathology.

Our permeability assay is based on T1 weighted ICE-MRI after instillation via transurethral catheter of FDA approved agents, Gadobutrol and Ferumoxytol in a proprietary mixture, of which only the smaller molecular weight Gadobutrol (604.71 Daltons) diffuses differentially into lesioned and normal areas of the bladder wall to cause differences in brightness while the larger molecular weight, Ferumoxytol is retained in the bladder lumen to darken it for the improved image contrast of bladder wall.

Objective: a cross-sectional prospective study on previously cystoscoped 10 HIC patients 10 NHIC patients, and 10 asymptomatic controls, to test the Hypothesis: ICE-MRI based bladder mucosal permeability descends from HIC>NHIC> controls.

Aim 1: To calibrate the ICE-MRI based bladder mucosal permeability assay on HIC, NHIC patients and asymptomatic subjects who have normal cystoscopic findings.

2. * **Describe the relevant prior experience and gaps in current knowledge including preliminary data. Provide for the scientific or scholarly background for, rationale for, and significance of the research based on existing literature and how it will add to existing knowledge:**

While the etiology of IC/BPS is multifactorial, there is published evidence that supports inflammation mediated impairment of the bladder mucosal permeability as a major pathophysiological cause of HIC. Despite this, bladder mucosal permeability is yet to be measured reliably and without evoking pain. This confusion in the true diagnosis of HIC have also hampered the drug development as reflected by several failed recent clinical trials of anti-inflammatory drugs. While the diagnosis of any disease is challenging, Vickie Ratner, an IC/BPS patient herself and ex-President of interstitial cystitis association once lamented that it often takes 5 doctors to make the correct diagnosis of IC/BPS. Therefore, a bladder permeability assay can complement conventional cystoscopy-based phenotyping of IC/BPS to reduce delay in getting appropriate medical care and in the objective selection of bladder-centric IC/BPS patients for testing of anti-inflammatory drugs.

Scientific premise- This project seeks to translate the intravesical-contrast enhanced magnetic resonance imaging (ICE-MRI) based assay of bladder permeability to clinic and these translation efforts are premised on the following published evidences:

1) Bladder mucosal permeability is a key pathophysiological mechanism in a subset of IC/BPS patients

2) the previously reported augmented diffusion of instilled drugs and radiolabeled antibodies into the lesioned area of human bladder is visualized by the augmented diffusion of instilled Gadobutrol into lesioned areas by ICE-MRI in a radiation-free

manner.

We recently reported augmented, paracellular diffusion of instilled Gadobutrol into lesioned areas of rat bladder(PMC7509285; PMC6028942; PMC8484474)

# Study Design

1. **Total number of subjects to be enrolled at this site (enter -1 for chart reviews, banking, registries):**
   30

2. **Describe and explain the study design:**
   Study design: Cross-sectional prospective study on consented, age matched 10 HIC, 10 NHIC, and 10 asymptomatic controls.

   To demonstrate the clinical feasibility of our MRI based permeability assay, we propose to first calibrate the MRI based bladder permeability assay by detecting significant differences in Gadobutrol permeability between 10 HIC patients (true-positive for bladder permeability) and 10 asymptomatic patients with no abnormal cystoscopic findings (true-negative for bladder permeability). After calibrating the MRI based bladder permeability assay, we will have 10 NHIC patients submit to the assay to determine if they have either low or high Gadobutrol permeability.

3. **Describe the primary and secondary study endpoints:**
   Primary endpoints:
   1) significant difference between the Gadobutrol permeability of HIC patients and controls
   2)Stratification of 10 NHIC patients into either low or high Gadobutrol permeability groups

   Secondary endpoint:
   1) safety and tolerability of instilled Gadobutrol and Ferumoxytol mixture

2) correlation of Gadobutrol permeability with the urine levels of cytokines and chemokines analyzed by a multiplex approach

**4. Provide a description of the following study timelines:**

**Duration of an individual subject's active participation:**

2 weeks

**Duration anticipated to enroll all subjects:**

2 years

**Estimated date for the investigator to complete this study (complete primary analyses):**

8/28/2024

**5. List the inclusion criteria:**

18-80 years old subjects from both genders and an IC/BPS diagnosis with a cystoscopic finding of Hunner lesions or absence and also have the following:
1) Pain (suprapubic, pelvic, urethral, vaginal or perineal) associated with bladder storage symptoms and pain on bladder filling that is relieved upon emptying
2) Urgency or nocturia (average of >1 nocturnal void over 3 consecutive days on bladder diary). The O'Leary-Sant Interstitial cystitis symptom index (ICSI) and Interstitial cystitis problem index ICPI are valid and reliable measures of IC/PBS symptoms, and only IC/PBS patients with scores of ICSI of > 9 and an ICPI > 8 will be recruited.
Age matched controls with no abnormal cystoscopic findings and with no storage LUTS will be recruited.

**6. List the exclusion criteria:**

1) Patients with urinary incontinence, suspicion for UTI on urine dipstick, history of recurrent UTIs, or history of spinal cord injury. Notwithstanding the fact that chronic

bladder inflammation of IC/BPS patients evokes higher bladder permeability to instilled radiolabeled sodium chloride than acute inflammation of UTI patients, we plan to exclude UTI patients as a confounding factor to rigorously establish the link between Hunner lesion and bladder permeability.

2) Patients with current diagnosis or previous history of urologic malignancy, prior bladder augmentation surgery, pelvic radiation, serum creatinine >1.5mg/dl, diabetes mellitus, untreated hypertension, and proteinuria.

3) Participants in whom magnetic resonance imaging (MRI) is contraindicated including, but not limited to, those with a pacemaker, presence of metallic fragments near the eyes or spinal cord, or cochlear implant, any other implanted MRI non-compatible device of any type (cardiac pacemaker, sacral neuromodulation device, and shunt)

4) Patients who are claustrophobic, cannot sign informed consent, or have a past allergic reaction to either Gadobutrol or Ferumoxytol and any history of allergic reaction to any intravenous iron product.

5) Women of child-bearing age who are pregnant or plan to become pregnant (urine pregnancy test will be performed for premenopausal women with no history of prior hysterectomy)

6) Patients who cannot safely refrain from taking any analgesics or steroidal/non-steroidal anti-inflammatory or immunosuppressive drugs for one week preceding the MRI to avoid any confounding effect of anti-inflammatory drugs on bladder permeability.

7) Any patient with a history of allergic reaction to any intravenous iron product."

**7. Will children or any gender, racial or ethnic subgroups be explicitly excluded from participation?**

● **Yes** ○ No

*** Identify the subgroups and provide a justification:**

Children will be excluded as the disease in question is only reported in adults above the age of 18 years

**8. Describe the power analysis used and cite your method of statistical analysis. If a power analysis is not possible, thoroughly justify the sample size required for the study, including appropriate literature citation (alternatively provide page reference in attached protocol):**

Sample size calculation for two sample with assuming equal variance and two-sided test where the difference is not equal to zero.

Numeric Results for Two-Sample T-Test Assuming Equal Variance

Alternative Hypothesis: $\delta \neq 0$

| Target Power | Actual Power | N1 | N2 | $\delta$ | $\sigma$ | Alpha |
|---|---|---|---|---|---|---|
| 0.80 | 0.85055 | 6 | 6 | 50.0 | 30.0 | 0.050 |
| 0.90 | 0.90156 | 7 | 7 | 50.0 | 30.0 | 0.050 |

Report Definitions

N1 and N2 are the number of items sampled from each population of HIC and SUI.

$\delta$ is the difference between population means at which power and sample size calculations are made.

$\sigma$ is the assumed population standard deviation for each of the two groups.

Alpha is the probability of rejecting a true null hypothesis.

Target Power is the desired power value (or values) entered in the procedure. Power is the probability of rejecting a false null hypothesis.

Actual Power is the power obtained in this scenario. Because N1 and N2 are discrete, this value is often
(slightly) larger than the target power.

Summary Statements

Power analysis tabulated in first row based on high permeability value of HIC in preliminary data shows that at least 7 patients in each cohort of HIC and controls will achieve 90% power at a significance level (alpha) of 0.050 to reject the null hypothesis of equal means when the population mean difference is 100 μM in Gadobutrol concentration of mucosa with a standard deviation of 30 μM using two sample t-test.

Power analysis supports small sample sizes for ICE-MRI because the permeability approach directly measures the concentration of Gadobutrol diffusing into bladder mucosa and thereby the method avoids the confounders associated with measuring the serum levels of the permeability probe.

# Research Activities

1. * **Provide a detailed description of all research activities (including screening and follow-up procedures) that will be performed for the purpose of this research study. This description of activities should be complete and of sufficient detail to permit an assessment of associated risks.**
After obtaining informed consent, subjects will be screened to determine if they meet the inclusion/exclusion criteria.

   STUDY VISITS:

   Visit 1 and Visit 2 (for cystoscopy if not recently performed): Potential subjects seen in the clinic as part of routine clinical care that meet inclusion and exclusion criteria will only participate in the study. Urine pregnancy and dip UA test (to screen for UTI) will be done on visit 1. Many of the patients screened for this study will have already had cystoscopy performed within the last 6 months as this is done to confirm the diagnosis of IC/BPS. These patients won't need cystoscopy and they wont return for a separate visit. However, if no cystoscopy has been performed within the past 6 months on enrolled subjects this will be performed on a return visit, visit 2. Visit 2 for cystoscopy will happen within 2-4 weeks of visit 1. Dip UA test (to screen for UTI) will be done on visit 2 prior to cystoscopy for those who have not had cystoscopy within the last 6 months. Again, cystoscopy won't be needed for those HIC and NHIC patients that have had cystoscopy within the past 6 months. While asymptomatic controls could include patients with other urologic diseases such as kidney stones or vaginal prolapse, these patients will need cystoscopy during visit 2 if no prior cystoscopy has been performed within the past 6 months. Thus, all patients will submit to visit 1 for screening and signing of informed consent, and visit 2 for cystoscopy will only be necessary for those who need cystoscopy if not performed within 6 months of completing informed consent on visit 1.

Visit 3 ICE-MRI: (or Visit 2 for those who didn't need a separate and current cystoscopy visit): Prior to catheterization and MRI, voided urine will be collected for urinalysis testing (to screen for UTI), urine pregnancy test in women who are of childbearing age, and urine that will be stored and tested for cytokine analysis at a later date. After intravesical instillation of 50 mL of saline and then contrast mixture, T1 weighted MRI will be performed and T1 relaxation rate of lesioned and normal areas of bladder wall will be measured to calculate the Gadobutrol permeability from the linear equation: $1/(\Delta T\ 1)=r1.[Gd]$ where r1 is the relaxivity of Gadobutrol at 3T ($4.3 \pm 0.7$ L/mmol/s) and [Gd] is the unknown Gadobutrol concentration diffusing into bladder mucosa.

MRI will be performed on a 60-cm wide bore 3T scanner (Siemens AG, Erlangen, Germany) with a 4-channel flexible and spinal coil placed over the bladder region of the subjects. We will use 3D FLASH sequence for scanning. Variability of urine production during scanning will be reduced by advising the subjects not to consume any oral fluids beginning 4 hours before the scheduled MRI. To reduce the variability in imaging from variable bladder distension in pre-instillation images, subjects will be asked to void before entering the scanner and urine collected for analysis of secondary endpoint. Subjects will be prepared for catheterization with an oral prophylactic dose of either ciprofloxacin, nitrofurantoin, or sulfamethoxazole/ trimethoprim (pending allergy profile or potential drug-drug interactions) and transurethral instillation of 2% lidocaine hydrochloride jelly. The urethral meatus will be prepped, and a 16 Fr foley catheter will be inserted into the bladder and the balloon inflated with 5 cc of water. Then, 50 mL of sterile saline will be instilled through the catheter, the catheter will be plugged, and the pre-instillation scan will be performed. Subsequently, the bladder will be fully emptied through the catheter and 50 mL of contrast mixture [302mg of Gadobutrol and 1.5mg Ferumoxytol] will be instilled in all subjects for acquiring the post-instillation scan as reported for pre-instillation scan. The subject will be repositioned to the same position in the scanner

for acquiring the pre-instillation and post-instillation scans of 15-30 minutes each and two T1 weighted image datasets will be linearly registered to the same subject.

The research nurse will phone the patient 24 hours after the MRI to monitor for any adverse events.

The antibiotics/lidocaine jelly described here are standard of care for cystoscopy and catheterization procedures and are not specific to this research study.

**2. Upload a copy of all materials used to collect data about subjects: (Attach all surveys, interview/focus group scripts, and data collection forms except for case report forms, SCID or KSADS):**

| | Document | Category | Date Modified | Document History |
|---|---|---|---|---|
| View | MR screener form(0.01) | Data Collection | 7/8/2022 | History |
| View | IC Questionnaires(0.01) | Data Collection | 5/12/2022 | History |

**3. * Will blood samples be obtained for research purposes?**

○ Yes ● **No**

# Consent Process

*Enter N/A in response to the following questions if a Waiver of Consent is requested for all research activities or if no subjects are being enrolled.*

1. * **Indicate where the consent process will take place and at what point consent will be obtained:**
   Informed consent will be obtained by Dr Chermansky, a listed licensed physician investigator, in his female urology clinic at Magee Womens Hospital Suite 2541. Informed consent will be obtained prior to initiating any testing.

2. * **Describe the steps that will be taken to minimize coercion and undue influence, including assurance that there is sufficient time for subjects to make an informed decision:**
   Dr. Chermansky will review the informed consent with each patient, and the patient will have ample time to read the informed consent document and ask any questions prior to signing the consent. Should the patient desire more time to decide about participating in the study, the patient will be given both a copy of the consent document to take home and the phone number of the research nurse to contact. Once the consent document is signed by the patient, the original document will be placed in the patient's research file and a copy of the consent will be provided to the subject. A note documenting that informed consent was obtained will be recorded in the patient's research file.

3. **For studies that involve multiple visits, describe the process to ensure ongoing consent:**
   Patients who have consented to participate in the study will be reminded of the

option to withdraw from the study at any point prior to study completion. As such, ongoing consent will be ensured.

4. * **Steps to be taken to ensure the subjects' understanding:**
Each subject will be asked questions to confirm their understanding of the research, and each subject will be asked to summarize the activities involved in the research study, including the number of visits required in the study and all procedures involved. These procedures include cystoscopy (if not done within the last 6 months), and catheterization, bladder instillation of Ferumoxytol and Gadobutrol through the catheter, and MRI. Finally, each patient will be asked to recall the potential adverse events from each procedure.

5. * **Are you requesting an exception to the IRB policy related to the informed consent process:**
○ Yes ● **No**

# Consent Forms

## 1. Consent Forms:

| | Document | Category | Date Modified | Documer History |
|---|---|---|---|---|
| View | Chermansky MRI for IC BPS Informed Consent 8-13.22.2022_Version_0.01_Version_0.02_Version_0.01.docx(0.01) | Consent Form | 8/13/2022 | History |

Refer to the following templates and instructional documents:

- Guidance - Consent Wording
- Template - Consent Document - Short Form
- HRP-090 - SOP - Informed Consent Process for Research
- HRP-091 - SOP - Written Documentation of Consent

# Medical Records

1. You are required to submit this study to the Research Informatics Office, Health Record Research Request (R3). Per UPMC Policy HS-RS0005, all research projects that access or involve UPMC electronic protected health information (e-PHI) must be submitted to R3, with the exception of clinical trials that are contracted through the UPMC Office of Sponsored Programs and Research Support (OSPARS).

   Complete the R3 intake form available at http://rio.pitt.edu/services. An R3 representative will conduct a review. You will be notified once your R3 review is complete or if anything further is needed.

*** Describe the protected health information that will be collected from the covered entity and/or the research derived information that will be placed into the medical records:**

Disease history,
Cystosopy findings,
Any drug treatment,
MRI scan results,
Dip Urinalysis results,
Urine pregnancy test results,
The signed informed consent document

The dip urinalysis results, urine pregnancy test results, and the MRI scan results will be placed in the medical record

# Electronic Data Management

1. * **Will only anonymous data be collected** (select **NO** if identifiers will be recorded **at anytime during the conduct of the study)?**

   ○ Yes ● **No**

**Select all identifiers to be collected during any phase of the research including screening:**

| | | | |
|---|---|---|---|
| **Name:** | ☑ | **Internet Protocol (IP) Address:** | ☐ |
| **E-mail address:** | ☑ | **Web Universal Resource Locators (URLs):** | ☐ |
| **Social security #:** | ☐ | **Social security # (for Vincent payment only):** | ☑ |
| **Phone/Fax #:** | ☑ | **Full face photo images or comparable images:** | ☐ |
| **Account #:** | ☑ | **Health plan beneficiary #:** | ☐ |
| **Medical record #:** | ☑ | **Device identifiers/serial numbers:** | ☐ |
| **Certificate/license #:** | ☐ | **Vehicle identifiers/serial #/license plate #:** | ☐ |
| | | **Biometric identifiers, finger and voice prints:** | ☐ |

* **a: Will you be collecting any of the following location data: geographic subdivisions smaller than a State such as street address, city, county, precinct, zip, geocodes, etc.?**

* **b: Will you be collecting any date information such as birth date, death, admission, discharge, date of surgery/service?**

**c: List any other unique identifying numbers, characteristics or codes related to an individual that are to be collected:**

**d: Will you be collecting any data subject to the General Data Protection Regulation (GDPF**

* **e: Provide a justification for recording Social Security numbers including why it's required where it's stored, how it's protected and who will have access:**

| | |
|---|---|
| * **For ALL identifiable data collected, will you be coding the data by removing the identifiers and assigning a unique study ID/code to protect the identity of the participant?** | ● **Yes** ○ **No** |
| * **Will the data be** HIPAA de-identified**?** | ● **Yes** ○ **No** |
| * **Briefly describe your plan to store coded data separately from the identifiable data:** | Only the research coordinator of this research study will have access to patient records with identifiable data which will be stored in password-protected computer file in desktop computer of research coordinator. This will data will be kept separately from the de-identified data. |

2. **During this study, will restricted data as defined by the University's Data Risk Classification matrix (** https://www.technology.pitt.edu/security/data-risk-classification-and-compliance **) be processed, stored, or transmitted?**
   ● **Yes** ○ No

3. * **During this study, will sensitive data (**https://www.hrpo.pitt.edu/electronic-data-security**) be collected where disclosure of identifying information could have adverse consequences for subjects or damage their financial standing, employability, insurability, educational advancement, reputation or place them at risk for criminal or civil liability?**
   ● **Yes** ○ No

4. * **Select all locations where data will be stored or archived(including e.g.,** personal / employer laptop or desktop)**: If you have access to University owned or controlled resources, facilities, or repositories, such as computer servers, please choose that option to comply with the** Research Data Management Interim Policy R1 14.

**Please note that to address Research Security Requirements, University data must be stored in University owned, controlled, or approved repositories, such as Pitt OneDrive. If UPMC or external electronic repositories must be used, they must be approved by Pitt IT.**

| | Storage Device | Description | Identifiable Data | Sensitive Data | De-Identified/Anonymous Data |
|---|---|---|---|---|---|
| View | PITT owned desktop, laptop or other device | The desktop computers of the research coordinator and the principal investigator | yes | yes | yes |

5. * **Select all technologies used to collect data, interact with subjects, or store subject data. Technologies selected in this section may require a Vendor Security Risk Assessment, which can be requested** here.

N/A

# Data Safety and Monitoring

1. * **Describe your plan to periodically evaluate the data collected regarding both harms and benefits to determine whether subjects remain safe. The plan might include establishing a data monitoring committee and a plan for reporting data monitoring committee findings to the IRB and the sponsor:**
The monitoring of recruitment, data collection, and adverse events will occur at least quarterly but may occur more frequently.
Monitoring will be followed to ensure the protection of the rights and welfare of study subjects, to ensure that the clinical investigational plan is followed, and to ensure compliance with the federal regulations and regulatory bodies (FDA and IRB).
Adverse events (AEs) will be reported in accordance with the Department of Health and Human Services (DHHS) code of federal regulations (Title 45, Part 46).
(http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm)
The conduct of the clinical study will be supervised through a process of on-site monitoring for data completeness and for adverse events. On-site monitoring will be implemented as necessary throughout the course of the study. PI will provide direct access to source data/documents for study-related monitoring, audits, IRB review, and regulatory inspection.

What will be monitored: Adverse events (AEs) will be reported in accordance with the Department of Health and Human Services (DHHS) code of federal regulations (Title 45, Part 46).
(http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm). Adverse events, defined as "unanticipated problems", have been specified for this trial. The list of reportable AEs will be approved by PI.

Who will complete the monitoring: The PI and the research coordinator will complete the monitoring.

How often the monitoring will occur: In-person monitoring will occur for an immediate hour after MRI. Furthermore, the research nurse will phone the patient 24 hours after the MRI to monitor for any AEs. There are two categories of AEs: 1) Serious Adverse Events and 2) Adverse Events. Serious adverse events are required to be reported within 72 hours of occurrence or knowledge of the event by PI. Adverse events not in the "serious" category, but judged to be "severe" or "life threatening" are also subject to the 72 hours reporting requirement. The report will document that a review of data and outcomes took place on a given date. It will also inform Investigators of the PI's conclusion with respect to progress or need for modification of the protocol. Potential Complications of intravesical Instillation of moderate or minor concern that is reportable to IRB and funding agencies at set intervals: recurrent urinary tract infections, urinary retention, urinary incontinence, worsened urinary urgency and urinary frequency symptoms not associated with UTI, cystitis, and hematuria.

**2. * Describe your plan for sharing data and/or specimens:**

The de-identified data will be shared with Lipella since this grant is funded through an SBIR by the NIH. Also, the de-identified results of this study, when finalized, will be submitted for publication and hopefully published.

The patients' identities may be disclosed to the governing health authorities or the FDA (Food and Drug Administration) if study records are inspected.

Appropriate precautions will be taken to maintain confidentiality of medical records and personal information.

Although there is currently no data sharing plan, should I decide to share data in the

future, I will contact the Office of Sponsored Programs before sharing de-identified research data/materials to determine whether an agreement needs to be executed.

3. **If any research data is collected, stored, or shared in a paper format, address what precautions will be used to maintain the confidentiality of the data:** Paper consent forms will be stored securely in a locked cabinet with access restricted to only study team members.

# Specimens and Related Data

1. * **Data and Specimens will be stored:**
   Long-term banking (e.g., indefinitely)
   Shared with others outside this institution (includes dbGap)

2. * **Indicate the type of specimen, describe where stored, and for how long:**
   Urine samples collected as part of the study will be collected and stored at the Urology Research Labs in UPMC Montefiore Hospital E313 for the duration of the study.

3. * **How the specimens will be accessed and who will have access to the specimens:**
   Urine samples will only be accessed by study investigators to correlate MRI image findings with the urine levels of proteins.

4. * **List the data to be stored or associated with each specimen:**
   Data to be associated with each specimen includes: diseases status, MRI findings, and cystoscopy status

5. * **Describe the procedures to release data or specimens, including the process to request a release, who can obtain data or specimens, the data to be provided with the specimens:**
   All requests for data or specimens must be approved by the the PI and Lipella. Researchers from other institutions may request access to specimens in writing via a formal proposal to the PI and Lipella. If additional data related to the specimens is

also requested, that request must also be included in the proposal and approved by the PI and Lipella. All data is de-identified.

# Risk and Benefits

## 1. * Enter all reasonably foreseeable risks, discomforts, hazards, or inconveniences to the subjects related to subjects' participation in the research:

View

| | |
|---|---|
| **Research Activity** | **Catheterization** |
| **Common Risks** | **- Urinary Tract Infection - Bleeding - Bladder or urethral pain during the catheterization - Pain with urination after the procedure** |
| **Infrequent Risks** | **- Injury to the urethra (the tube that carries urine out of the body) when the catheter is inserted incorrectly - Narrowing of the urethra from a urethral stricture that may develop after injuring the urethra during catheterization** |
| **Other Risks** | **none** |

View

| | |
|---|---|
| **Research Activity** | **Urine pregnancy test** |
| **Common Risks** | **none** |
| **Infrequent Risks** | **breach of confidentiality** |
| **Other Risks** | **none** |

View

| | |
|---|---|
| **Research Activity** | **Urine dipstick test** |
| **Common Risks** | **none** |
| **Infrequent Risks** | **none** |
| **Other Risks** | **none** |

View

| | |
|---|---|
| **Research Activity** | **Gadobutrol** |

| | |
|---|---|
| **Common Risks** | **Bladder instillation drastically reduces side effects associated with the approved intravenous route but Gadobutrol can cause urinating less than usual or not at all; drowsiness, confusion, mood changes, increased thirst, loss of appetite; swelling, weight gain, shortness of breath; seizures (convulsions); breathing problems; pounding heartbeats or fluttering in your chest; or severe pain, burning, or irritation around urethra.** |
| **Infrequent Risks** | **headache nausea vomiting feeling unwell (malaise) dizziness abnormal or unpleasant taste in your mouth feeling hot numbness or tingly feeling itching or rash skin redness injection site reactions (cold feeling, warmth, pain, or burning).** |
| **Other Risks** | **none** |

View

| | |
|---|---|
| **Research Activity** | **MRI** |
| **Common Risks** | **MR images are made without using any ionizing radiation, so you are not exposed to the harmful effects of ionizing radiation as in X-ray. But while there are no known health hazards from temporary exposure to the MR environment, the MR environment involves a strong, static magnetic field, a magnetic field that changes with time (pulsed gradient field), and radiofrequency energy, each of which carry specific safety concerns: The strong, static magnetic field will attract magnetic objects (from small items such as keys and cell phones, to large, heavy items such as oxygen tanks and floor buffers) and may cause damage to the scanner or injury to the patient or medical professionals if those objects become projectiles. Careful screening of people and objects entering the MR environment is critical to ensure nothing enters the magnet area that may become a projectile.** |
| **Infrequent Risks** | **The magnetic fields that change with time create loud knocking noises which may harm hearing if adequate ear protection is not used. They may also cause peripheral muscle or nerve stimulation that may feel like a twitching sensation. The radiofrequency energy used during the MRI scan could lead to heating of the body. The potential for heating is greater during long MRI examinations. Some patients find the inside of the MRI scanner to be uncomfortably small and may experience claustrophobia.** |

| | |
|---|---|
| **Other Risks** | **If a bladder tumor is identified by MRI, this will be disclosed to the subject and the subject will be directed to seek appropriate care with another urologist for treatment.** |

View

| | |
|---|---|
| **Research Activity** | **collection of private identifiable information** |
| **Common Risks** | **none** |
| **Infrequent Risks** | **risk of breach of confidentiality** |
| **Other Risks** | **none** |

View

| | |
|---|---|
| **Research Activity** | **Ferumoxytol** |
| **Common Risks** | **Bladder catheterization for instillation of Ferumoxytol and very low dose eliminates toxicity associated with injection of Ferumoxytol** |
| **Infrequent Risks** | **Low Blood Pressure Diarrhea, Headache, Nausea Dizziness Constipation Swelling in your hands or feet** |
| **Other Risks** | **none** |

View

| | |
|---|---|
| **Research Activity** | **Cystoscopy (if needed)** |
| **Common Risks** | **urinary tract infection (UTI), bleeding, bladder or urethral pain during the procedure, and pain with urination after the procedure** |
| **Infrequent Risks** | **If a bladder tumor is identified by cystoscopy, this will be disclosed to the subject and the subject will be directed to seek appropriate care with another urologist for treatment.** |
| **Other Risks** | **none** |

**2. * Describe the steps that will be taken to prevent or to minimize risks:**

To ensure the safe and efficient use of MRI in human subject research, a set of

policies and procedures that are compliant with the American College of Radiology's "white paper" on MR Safety. All potential participants are screened twice, by trained staff, for potential contraindications to MRI (e.g., pacemaker, aneurysm clip, ear implants, etc.). Participants with a history of metal work (e.g., welding) or injury related to metallic foreign matter, will undergo a radiograph of the affected area to ensure the safety of proceeding with MR scanning. All radiographs will be interpreted by a radiologist. The potential risks related to
MR scanning will be further minimized in the following manner:

1. Claustrophobia from MR imaging will be reduced by thoroughly explaining the procedure and nature of the scanner to participants in advance of scanning. Participants who have a significant history of claustrophobia will not be entered in the study. Furthermore, the study will be terminated at the participant's request.

2. Participants with contraindications to MR scanning, including but not limited to aneurysm clip, pacemaker, intraocular metal, and cochlear implant, will be excluded from the study.

To prevent risk of infection from catheterization and cystoscopy, urine will be checked for possibility of urinary tract infection by dipping paper strips in collected urine specimen cups. Furthermore, all subjects will receive a prophylactic antibiotic and a sterile antiseptic will be applied to the urethral opening before catheterization and cystoscopy. Viscous lidocaine per gel will be inserted per urethra prior to cystoscopy to minimize pain with the procedure. Any systemic adverse event occurring after intravesical instillation will be reported and patients will be properly investigated and treated.

Patients will be monitored during the bladder instillation and MRI procedure. Appropriate care will be provided to any patient who experiences an adverse event while being treated. Patients are encouraged in the consent form to report adverse

events to the investigators, and treatment will be administered as needed. Patients will be advised regarding the importance of reporting any adverse events to their investigator/subinvestigator or the study coordinator so that the appropriate medical treatment can be administered to prevent life threatening or fatal adverse events. The results of all study tests will be discussed with the patient and this information will be protected under the University, Hospital and federal HIPAA policies. Medical records will be considered confidential and are stored in a locked cabinet in the administrative office of Dr. Chermansky. The only persons with access to these records will be the clinical principal investigator and his research team, representatives of the NIH, the National Monitoring Committee and the Institutional Review Board (IRB). Patients will not be identified in any report or publication of this study or its results without prior written permission. If patients are injured due to their participation on trial, immediate medical care will be provided by the clinical PI and resources of UPMC as outlined in the informed consent document.

The risk of loss of confidentiality also exists. Care will be taken to preserve confidentiality. Only research personnel will have access to patient records and patients will not be identified in any published study. The study database will be accessed by password protection only.

3. **Financial risks - will the subject or insurer be charged for any research required procedures?**

   ○ Yes ● **No**

4. **Describe the steps that will be taken to protect subjects' privacy:**

   The research intervention will be conducted in a private room. The collection of sensitive information about subjects is limited to the amount necessary to achieve the aims of the research, so that no unneeded sensitive information is being collected, drapes or other barriers will be used for subjects who are required to disrobe, etc.

5. **What steps will be taken in the event that a clinically significant, unexpected disease or condition is identified during the conduct of the study:**
If study procedures identify UTI, pregnancy (through urine test), or bladder tumor (through MRI or cystoscopy), we will disclose the information to the enrolled subject. UTI will be treated by the PI. If the female subject is found to be pregnant she will be directed to seek care to an obstetrician of her choice. If a bladder tumor is found, the subject will be directed to seek appropriate care with another urologist who specialized in bladder tumors.

6. **Describe the potential benefit that individual subjects may experience from taking part in the research or indicate if there is no direct benefit. Do not include benefits to society or others:**
There is no benefit to the individual subjects to participate in this research study.

7. **Do you anticipate any circumstances under which subjects might be withdrawn from the research without their consent?**
● **Yes** ○ No

* **Describe the circumstances and any procedures for orderly termination:**
The subject may be removed from the research study by the researchers if the study investigators on further review of the subject's information determine that the study participation of the subject may not be in the interest of study goals or the subject's safety

8. **Describe procedures that will be followed when subjects withdraw from the research, including partial withdrawal from procedures with continued data collection and data already collected:**

Any identifiable research or medical information recorded for, or resulting from, participation in this research study prior to formal withdrawal of consent may continue to be used and disclosed by the investigators for the purposes described above.

# Conflict of Interest

## Institutional Financial Interests

1. * **To the best of your knowledge, has the University of Pittsburgh optioned or licensed technology that will be tested or evaluated in this research?**

   ○ Yes ○ No

# Ancillary Reviews

1. **Ancillary reviews or notifications selected below are required based on previous answers to questions. If a selection is incorrect, return to the appropriate page and adjust the answers to questions on that page:**

- [ ] Conflict of Interest (**COI**)
- [ ] Clinical and Translational Research Center (**CTRC**)
- [x] Data Security
- [ ] Honest Broker
- [x] UPMC Investigational Drug Service
- [ ] Pitt Medical School Review
- [ ] Pitt Nursing School Review
- [x] Pitt+Me
- [ ] IND & IDE SUPPORT (**IIS**)
- [ ] Radioactive Drug Research Committee (**RDRC**)(study involves the evaluation or use of procedures that emit ionizing radiation)
- [ ] RCCO Business **Manager** (required for industry sponsored studies)
- [ ] Religious Directives
- [ ] Scientific Review
- [x] Health Record Research Request (**R3**) (required if using UPMC clinical data and authorization for other UPMC data sources for research)
- [x] UPMC Sponsored Clinical Trials and Partnerships (using UPMC facilities and/or UPMC patients during the conduct of the study)

2. **Additional ancillary reviews the PI may choose to include as needed for the research:**

☐ Human Stem Cell Oversight (**hSCRO**)

☐ Institutional Biosafety Committee (**IBC**)(study involves deliberate transfer of recombinant or synthetic nucleic acid molecules)

# Good Clinical Practice (GCP) Training

1. * **Regardless of funding source, is this study a clinical trial** (as defined by the NIH)**?**
   ● **Yes** ○ No

# ClinicalTrials.gov Information

*Visit the University of Pittsburgh Office for ClinicalTrials.gov website or contact ctgov@pitt.edu for further information.*

1. * **Was this study registered, or will it be registered, on ClinicalTrials.gov?**
   ● **Yes** ○ No

2. * **Is the University of Pittsburgh or UPMC the Sponsor Organization for this study record?**
   ● **Yes** ○ No

   * **Who will be the Responsible Party for this study record?**

   Principal Investigator of this IRB application

# Clinical Study Registry (CSR)

*Visit the Health Sciences managed Clinical Trials Office website or contact CTOHelp@pitt.edu for further information regarding health sciences studies that must be registered.*

1. * Has this study been registered with Clinical Study Registry maintained by Pitt's Clinical Trials Office within the Health Sciences?

# Supporting Documents

1. **Attach any additional supporting documents not previously uploaded. Name the documents as you want them to appear in the approval letter:**

| Document | Category | Date Modified | Document History |
| --- | --- | --- | --- |
| There are no items to display | | | |

# Add Drug Information

1. **Select the drug:**
   Ferumoxytol

   If you cannot find the drug in the list above, enter its information here:
   **Generic name:**

   **Brand name:**

2. * **Purpose of their use:**
   Add negative contrast in MRI after instillation in the bladder. Instead of the approved intravenous dose of 510mg for Ferumoxytol, we will instill only 1.5mg in bladder of human subjects via catheter. The proposed dose is 340times lower than the approved intravenous dose of 510mg for Ferumoxytol.

3. * **FDA status:**
   Approved drug or biologic being **evaluated for a new** indication, population, route of administration, or dosage level not specified in the FDA approved labeling

   * **Does the evaluation significantly increase the risk (or decrease the acceptability of risk) compared to the approved use?**
   ○ Yes ● **No**

*** Will data be reported to the FDA in support of a new indication, significant change in labeling or advertising?**

○ Yes ● **No**

**4. Attach files related to this drug:**

| | Document | Category | Date Modified | Document History |
|---|---|---|---|---|
| View | package insert(0.01) | Drug Attachment | 4/7/2022 | History |

Attachments should include a copy of the FDA-approved package label or Investigator Brochure.

# Add Drug Information

1. **Select the drug:**
   Gadobutrol

   If you cannot find the drug in the list above, enter its information here:
   **Generic name:**
   Gadobutrol

   **Brand name:**
   Gadavist

2. *** Purpose of their use:**
   Gadobutrol ( Gadavist) is approved by FDA for intravenous use during MRI, we plan to instill in the bladder at 14 times lower dose than the approved dose of 0.1mmol/kg or 60.2mg/kg. We will instill only 302mg in 50mL of sterile water for injection in the bladder of subjects and the administered dose comes out to be 4.31mg/kg for a 70kg adult, nearly 14 times lower than the FDA-approved intravenous dose of 60.4mg/kg.

3. *** FDA status:**
   Approved drug or biologic being **evaluated for a new** indication, population, route of administration, or dosage level not specified in the FDA approved labeling

   *** Does the evaluation significantly increase the risk (or decrease the acceptability of risk) compared to the approved use?**
   ○ Yes ● **No**

*** Will data be reported to the FDA in support of a new indication, significant change in labeling or advertising?**

○ Yes ● **No**

## 4. Attach files related to this drug:

| | Document | Category | Date Modified | Document History |
|---|---|---|---|---|
| View | package insert(0.01) | Drug Attachment | 4/7/2022 | History |

Attachments should include a copy of the FDA-approved package label or Investigator Brochure.

# Add Storage Information

1. * **Select a Storage Type:**
   PITT owned desktop, laptop or other device

2. **Description:**
   The desktop computers of the research coordinator and the principal investigator

3. * **Will identifiable data be stored in this location?**
   ● **Yes** ○ No

4. * **Will sensitive data be stored in this location?**
   ● **Yes** ○ No

   * **Define your encryption methods:**
   - **BitLocker (Windows)** (Turn on device encryption)
   - **File Vault (Mac)** (Use FileVault to encrypt the startup disk on your Mac)
   - **SecureZIP** (SecureZIP: Getting Started (Windows) | University of Pittsburgh)

   BitLocker is used for the Windows desktop computers of both the research coordinator and the PI

5. **Will de-Identified or anonymous data be stored in this location?**

● Yes ○ No

6. * Is anti-virus software installed and up to date on all devices and are the operating systems kept up-to-date on all devices?

● Yes ○ No

7. Provide additional information as needed:

# Risk

1. * **Research Activity:**
   Catheterization

2. **Common Risks:**
   - Urinary Tract Infection
   - Bleeding
   - Bladder or urethral pain during the catheterization
   - Pain with urination after the procedure

3. **Infrequent Risks:**
   - Injury to the urethra (the tube that carries urine out of the body) when the catheter is inserted incorrectly
   - Narrowing of the urethra from a urethral stricture that may develop after injuring the urethra during catheterization

4. **Other Risks:**
   none

# Risk

1. * **Research Activity:**
   Urine pregnancy test

2. **Common Risks:**
   none

3. **Infrequent Risks:**
   breach of confidentiality

4. **Other Risks:**
   none

# Risk

1. * **Research Activity:**
   Urine dipstick test

2. **Common Risks:**
   none

3. **Infrequent Risks:**
   none

4. **Other Risks:**
   none

# Risk

1. * **Research Activity:**
   Gadobutrol

2. **Common Risks:**
   Bladder instillation drastically reduces side effects associated with the approved intravenous route but Gadobutrol can cause

   urinating less than usual or not at all;
   drowsiness, confusion, mood changes, increased thirst, loss of appetite;
   swelling, weight gain, shortness of breath;
   seizures (convulsions);
   breathing problems;
   pounding heartbeats or fluttering in your chest; or
   severe pain, burning, or irritation around urethra.

3. **Infrequent Risks:**
   headache
   nausea
   vomiting
   feeling unwell (malaise)
   dizziness
   abnormal or unpleasant taste in your mouth
   feeling hot
   numbness or tingly feeling

itching or rash
skin redness
injection site reactions (cold feeling, warmth, pain, or burning).

**4. Other Risks:**

none

# Risk

1. * **Research Activity:**
   MRI

2. **Common Risks:**
   MR images are made without using any ionizing radiation, so you are not exposed to the harmful effects of ionizing radiation as in X-ray. But while there are no known health hazards from temporary exposure to the MR environment, the MR environment involves a strong, static magnetic field, a magnetic field that changes with time (pulsed gradient field), and radiofrequency energy, each of which carry specific safety concerns:

   The strong, static magnetic field will attract magnetic objects (from small items such as keys and cell phones, to large, heavy items such as oxygen tanks and floor buffers) and may cause damage to the scanner or injury to the patient or medical professionals if those objects become projectiles. Careful screening of people and objects entering the MR environment is critical to ensure nothing enters the magnet area that may become a projectile.

3. **Infrequent Risks:**
   The magnetic fields that change with time create loud knocking noises which may harm hearing if adequate ear protection is not used. They may also cause peripheral muscle or nerve stimulation that may feel like a twitching sensation.

   The radiofrequency energy used during the MRI scan could lead to heating of the body. The potential for heating is greater during long MRI examinations.

Some patients find the inside of the MRI scanner to be uncomfortably small and may experience claustrophobia.

**4. Other Risks:**

If a bladder tumor is identified by MRI, this will be disclosed to the subject and the subject will be directed to seek appropriate care with another urologist for treatment.

# Risk

1. * **Research Activity:**
   collection of private identifiable information

2. **Common Risks:**
   none

3. **Infrequent Risks:**
   risk of breach of confidentiality

4. **Other Risks:**
   none

# Risk

1. * **Research Activity:**
   Ferumoxytol

2. **Common Risks:**
   Bladder catheterization for instillation of Ferumoxytol and very low dose eliminates toxicity associated with injection of Ferumoxytol

3. **Infrequent Risks:**
   Low Blood Pressure
   Diarrhea,
   Headache,
   Nausea
   Dizziness
   Constipation
   Swelling in your hands or feet

4. **Other Risks:**
   none

# Risk

1. * **Research Activity:**
   Cystoscopy (if needed)

2. **Common Risks:**
   urinary tract infection (UTI), bleeding, bladder or urethral pain during the procedure, and pain with urination after the procedure

3. **Infrequent Risks:**
   If a bladder tumor is identified by cystoscopy, this will be disclosed to the subject and the subject will be directed to seek appropriate care with another urologist for treatment.

4. **Other Risks:**
   none