Study Protocol Cover Page

Study Protocol

ID: 2022P-000826

A Pilot Study to Assess Effects of Self-Administered Nitrous Oxide (SANO) on Urodynamic Study (UDS) Parameters

Please note: the Statistical Design included in this Protocol has been updated, and is included separately.

# PART B
# STUDY DESCRIPTION

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| **TITLE OF PROTOCOL** | **A Pilot Study to Assess the Effects of Self-Administered Nitrous Oxide (SANO) on Urodynamic Study (UDS) Parameters** |
| Principal Investigator | **Heidi Rayala, MD PhD** |

## B1. PURPOSE OF PROTOCOL

A Urodynamic Study (UDS) is a diagnostic procedure commonly performed by Urologists in the ambulatory setting to diagnose urinary dysfunction. A UDS is generally considered to have low morbidity, but patients may find it uncomfortable and anxiety provoking, partly because the study involves placing both a urethral and abdominal pressure catheter. The abdominal pressure catheters are placed in the rectum (for men and children) and the vagina (for women). Additionally, there are EMG electrodes placed at the anal sphincter, and in some patients (primarily children) these are needle electrodes. In adults, studies show that after a UDS, 15-26% of patients would not elect to undergo the UDS procedure again (Yokoyama, 2005). In children, distress rates can be as high as 61-71% during UDS (Herd, 2006). There have been multiple studies that have looked at ways to decrease the anxiety and discomfort experienced by patients during a UDS, including use of music, videos, and dimming of lights, all with varying effect. There are also studies that have looked at the use of medications such as ketamine or midazolam to reduce the pain and anxiety during UDS; however, in principle, UDS should not be performed when the patient is sedated as there is constant verbal feedback that is required throughout the testing process.

Nitrous oxide is an inhaled analgesic that is used in pediatric and adult populations for ambulatory procedures, and is largely viewed as effective and safe. Nitrous oxide also produces a dissociative euphoria and amnesia that could potentially improve patients' anxiety and experience of care during painful or anxiety provoking procedures. We have used patient self-administered nitrous oxide (SANO) in our ambulatory clinic at BIDMC for men undergoing prostate biopsies with good effect and no significant complications. SANO may offer an appealing option for patients who are reluctant to undergo an initial UDS or for those who have not tolerated the study in the past. What we do not know is whether a UDS performed under the influence of SANO will give study results that are accurate and reproduce the bladder function of the patient during their daily routine. In a pediatric population, both ketamine and midazolam have been shown to provide satisfactory sedation without impacting UDS values (Thevaraja, 2012); however, sedation with propofol does negatively impact outcome values (Merguerian, 2006). No studies to date assess whether the administration of SANO will negatively impact UDS results. It is possible that SANO will perform better than ketamine or midazolam, as it is anticipated SANO will reduce anxiety and perception of pain without causing a sedative effect.

We propose a pilot study with 25 patients (14 randomized) to compare the impact of SANO vs Oxygen on UDS parameters of patients undergoing routine UDS. Study procedures will take place in the Clinical Research Center (ST 802, Gryzmish 8). Our primary aim will be to assess whether SANO has any adverse effects on routinely measured UDS variables. We will assess whether

periprocedural SANO negatively impacts operator productivity or increases the difficulty in performing the UDS. A secondary aim will be to assess patient perceived pain and anxiety related to catheter placement and experience of SANO during the UDS.

**Specific Aims:**

**Aim 1:** To demonstrate that Self-Administered Nitrous Oxide (SANO) at the time of Urodynamic Study (UDS) does not significantly impact outcome variables during the study.

*Hypothesis 1.1: Administration of periprocedural SANO will not impact core UDS outcomes of "Bladder Capacity", "Maximum Flow Rate", and "Maximum Detrusor Pressure"*

*Hypothesis 1.2: Administration of periprocedural SANO will not significantly lengthen the time of the procedure*

*Hypothesis 1.3: Administration of periprocedural SANO will allow the operating APP to perform the procedure with the same ease as on those patients who do not have SANO.*

**Aim 2:** To assess effectiveness of SANO in decreasing patient perceived anxiety and pain related to UDS.

*Hypothesis 2.1: Administration of periprocedural SANO will improve patients' experience during the UDS as measured by VAS (visual analogue scale) score.*

*Hypothesis 2.2: Administration of periprocedural SANO will result in minimal side effects for the patients and will allow the patient to drive home independently.*

## B2. SIGNIFICANCE AND BACKGROUND FOR THE STUDY

**Burden of Urodynamic Study**

Urodynamic testing is an ambulatory procedure that is considered the gold standard for evaluating lower urinary tract symptoms (LUTS) in both female and male patients. Though not required for all patients with LUTS, a UDS can be particularly helpful in evaluating those patients who do not respond to first line treatment algorithms for LUTS. There are certain patient populations, such as children and adults with spina bifida, who require routine UDS evaluations to assess for worrisome changes that may result in damage to their urinary system. Many of these patients can develop an increasing reluctance to undergo UDS due to poor memories of prior experience. Studies have shown that up to 26% of patients are unwilling to undergo a future UDS (Yokoyama, 2005). In part, this dissatisfaction is due to the innate discomfort of the procedure; however, embarrassment and shame during UDS has also been found, especially in women (Yeung, 2014). Children may particularly bear a significant burden during UDS, with studies showing "serious" or "severe" distress in 61% of children undergoing UDS (Herd, 2006).

**Nitrous Oxide as an adjunct for Procedural Pain**

Inhaled nitrous oxide is commonly used for patient analgesia and anxiolysis outside of the US, and is gaining traction in the US. For example, use of nitrous oxide during labor occurs in 43% of Canadian deliveries and 62% of deliveries in the UK (Rooks, 2007). This has led to recent adoption and promulgation of nitrous oxide by AWHONN (Association of Women's Health Obstetric and Neonatal Nurses) as a "vital component in the provision of quality of maternity care" (Practice Brief, 2018). Nitrous oxide has also been adopted in US pediatric clinical settings, including Boston Childrens Hospital's Emergency Department.

**Administration:**

During self-administered nitrous oxide (SANO) a patient holds a gas mask to their own face, and works with the medical team to titrate the nitrous level to optimum concentration level. SANO is administered as a single agent of nitrous oxide, at concentrations <50%. At these levels, nitrous oxide is classified by the American Society of Anesthesiologists (ASA) as "mild sedation", which does not require the presence of anesthesia personnel, NPO status, nor escort home. Current literature states that "patients could safely operate a motor vehicle after N2O/O2 sedation" (Clark et al., 2020). An additional study performed by Hawkins, et al. similarly concludes that there does not appear to be any residual cortical effects from mild sedation with nitrous oxide. The recovery period was established to be three to five minutes following termination of nitrous oxide, and the expectation that participants would "return to normal at the first post-treatment determination (five minutes post-operative)" was confirmed. In each study, participants were given a 50-50 mixture of N2O/O2, and concentrations of NO2 between 35-50% (Clark et al., 2020). This closely mirrors our protocol's administration of nitrous oxide, as we are administering concentrations of 25-45%.

The Nitrouseal® system has an adjustable-concentration digital flowmeter and includes an FDA-cleared exhaled waste gas scavenger, the Miniscav®. The Nitrouseal® system includes a proprietary disposable single-use full-face mask and breathing circuit that collects and contains the exhaled nitrous gas before it is scavenged into the Miniscav®.

The Nitrouseal® has been used in urology since 2017 in procedures such vasectomies, cystoscopies, UroLift® implants, bladder biopsies, prostate biopsies and Botox injections, with reported improvement in patient anxiety, relaxation and comfort. However, there have been no controlled studies in the US that have studied the effects of nitrous oxide for UDS.

## B3. DESCRIPTION OF RESEARCH PROTOCOL

A. Study Design – Overview, Methods, Procedures

METHODS AND PROCEDURES:

**Screening**
After the Urologist has discussed and planned for office urodynamic study, a baseline examination by the clinical team for eligibility verification will be performed through a medical record review by a trained member of the research staff.

**Recruitment and Obtainment of Informed Consent**
A member of the research team will reach out by phone call and/or PatientSite email at least 1 week before their scheduled UDS. When discussing UDS with the attending urologist, the study will be verbally introduced to the patient and a flyer will be provided that includes laymen terms describing the protocol, risks and benefits, and information about enrollment. A phone call (or PatientSite message) by the research team will give a brief description of the research study. If the subject expresses interest in learning more about the study during the phone call (or in response to the PatientSite message), a member of the study staff will confirm eligibility to participate in the study based on pre-determined inclusion and exclusion criteria. If they do not qualify for the study, they will not be included, and will undergo a standard UDS only.
If the patient is eligible, informed consent procedures will be initiated using REDCap's Electronic Informed Consent (eIC) platform. Special care will be taken during the consent process to ensure subjects are fully competent and understand the nature of the questionnaires, as well as the randomization process (that they will not know at which point in the UDS they will be receiving Oxygen rather than SANO). A member of the study staff will review the entirety of the consent form and answer any questions before the subject provides a signature. If the subject desires to participate in the study, they will be asked to sign the electronic consent form on REDCap (Electronic Informed Consent (eIC)). Subjects will receive an email containing a PDF version of the eConsent signed by both the subject and the staff member obtaining the consent.

Efforts will be made to attain a mix of study participants in terms of racial/ethnic representation, which is reflective of BIDMC's patient population and the greater metropolitan Boston area: 63% white, 26% African American and 11% other.

**Baseline Assessment:**
Confirmation of a patient's eligibility and completed informed consent will be documented in REDCap before proceeding with study procedures. Then, patients will complete the Brief Pain Inventory (see attached) via REDCap questionnaire that is sent to the patient's email. The BPI is a well-validated measure that assesses intensity of current pain and interference of pain in the patient's life (Dworkin, 2005). If the patient does not complete the BPI electronically before the day of procedure, they will be offered the opportunity to complete it on the day of their procedure prior to the UDS.

**Randomization**

A UDS is comprised of two phases: a filling phase and a voiding phase. For the purposes of our study, subjects will undergo two "runs", one with SANO and one with Oxygen.
Subjects will be randomized to either:

- Group 1: First run with SANO, second run with Oxygen
- Group 2: First run with Oxygen, second run with SANO

The results of the randomization will not be disclosed to patients as part of the study (patient-blinded), or to the operator of the UDS (provider-blinded). The randomization module in REDCap will be used to randomize subjects between the two groups.

The catheters will be placed before the first run, and left in place through the second run (that is, the catheters will not be changed between the two runs). All subjects will receive SANO during catheter placement. The UDS will be performed by a BIDMC advanced care practitioner according to usual clinical practice. It is standard-of-care for patients to undergo two complete UDS runs:

- First run: Filling phase, voiding phase (~8 minutes)
- Second run: Filling phase, voiding phase (~8 minutes)

Therefore, we do not believe the utilization of two runs to be a significant increase in burden on the patient.

**Pre-procedure Evaluation**
On the day of the UDS, the patient will be brought to the exam room where pre-procedure vitals are obtained. The six-item State Trait Anxiety Inventory and the six-item Pain Catastrophizing Scale will be administered to assess patient's baseline pain and anxiety levels. Information of inhaled gas administration and how to self-administer will be explained to the patient using templated verbal instructions. It will be emphasized that if at any point during the procedure, the patient feels uncomfortable with the inhaled gas, the team will help remove the mask.

**Periprocedural Intervention**
The patient will be moved into the standard procedural positioning in the UDS chair. Explanation of the UDS procedure will be done in the routine manner preferred by the study technician (a Urology APP). An oxygen saturation monitor will be applied to the patient's finger and monitored throughout the procedure. The patient's heart rate will also be monitored.

During the procedure, the patient and their oxygen saturation levels will be monitored by a BLS-certified MA, RN, APP, or MD (separate from APP performing the procedure).

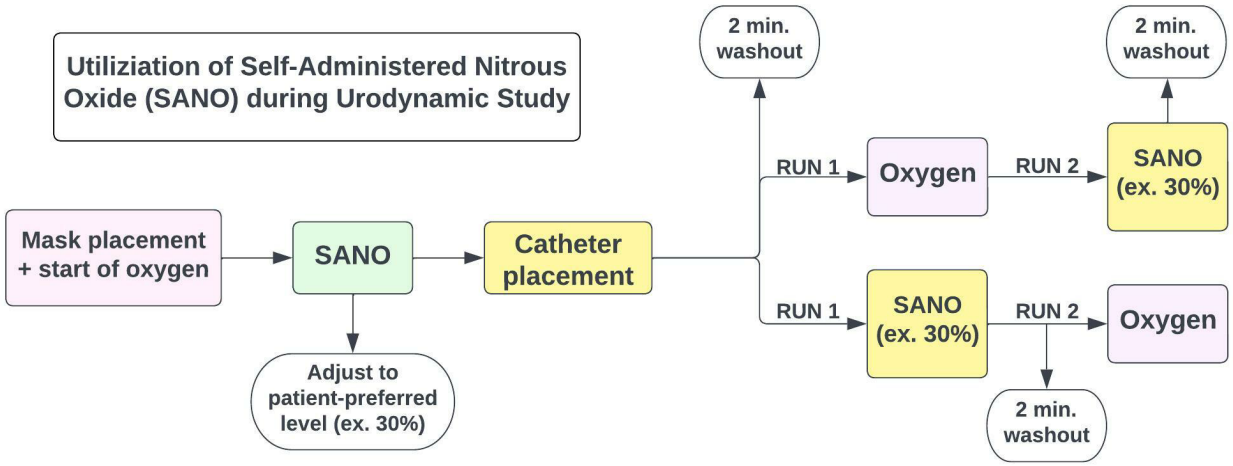
The inhalation gas mask will be positioned on the patient's face, and the patient will then be instructed to begin breathing as previously instructed. Initially, the patient will receive 100% oxygen at 10 liters/minute.

After the APP describes the procedure, all patients will have nitrous oxide turned on to 30%, ensuring that the patient is relaxed but still conversant through the procedure. The nitrous will be adjusted up or down based on the patient's response to the question "are you feeling the nitrous" and "are you happy at this level". The range will be between 25 - 45%, and will be recorded. This may take 2-3 minutes. The technician will then insert the urethral pressure catheter as well as the

abdominal catheter. We will then wash out with 100% oxygen for 2 minutes. We will perform the UDS study in the routine fashion, asking the patient to perform routine parameters such as cough, report of bladder fullness, and volitionally void. After the first run, we will again wash out with 100% oxygen for 2 minutes while we switch from SANO to oxygen (or vice versa depending on the randomization group).

At a single time-point during both runs, the operator handling SANO will ask the patient to complete a VAS-A and VAS-P. A laminated sheet will be held in front of the patient, and they will point to a number between 1 – 10 to signify their current level of anxiety (VAS-A) and pain (VAS-P). The number will be verbally confirmed by the operator handling SANO.

If at any point the patient is unhappy with gas inhalation, the observer will aid the patient in removing the mask. At the end of the procedure, the SANO group will be turned down to 0% nitrous oxide, and 100% oxygen will be administered through the mask for an additional 2-3 minutes as the patient is cleaned and post vitals obtained. Assessment of the "time in" and "time out" of the procedure room will be recorded.




Flowchart 1. Intraprocedural Study Activities

**Measuring gas flow:**
The maximum flow for this system is 19 L/min. The amount of gas flow is adjusted to match the patient's minute ventilation in order to maintain the black inspiration bag (inhalation reservoir) on the Flowmeter about 3/4 full during the procedure. This varies from patient to patient depending upon respiratory rate, and volume of each breath. Excess gas flows through the circuit and into the scavenger and has no effect on the patient.

**Periprocedural Data Collection**
The APP who performed the procedure will complete an Operator Survey (attached) to assess the ease of catheter placement and patient responsiveness during each run.
After the UDS, the patient will be moved to the recovery room for routine post-procedure vitals as well as completion of post-procedure STAI score and Situational Pain Catastrophizing Score (S-PCS)

on a tablet computer. The S-PCS was derived from the Pain Catastrophizing Scale (PCS), a validated questionnaire used to measure catastrophic thinking associated with pain. We will also ask if any side effects of nitrous oxide were experienced, including nausea, vomiting, dizziness, drowsiness. An additional question of whether the patient feels comfortable driving home independently will be assessed.

UDS is generally performed as an outpatient procedure and patients can drive themselves home. In our previous study, "Self-Administered Nitrous Oxide (SANO) During Transrectal Prostate Biopsy to Reduce Patient Anxiety and Pain" patients were allowed to drive home after study participation, without any adverse events or complications. Patients who do not have an escort planned after their UDS will be asked to perform two hand-eye coordination tests after completion of post-procedure surveys. First, the participants will be verbally instructed to extend one arm in front of them, and place one finger to the tip of their nose. After, the Trail-making test Part B will be administered. This test has been promulgated by the American Medical Association to screen for driving fitness. The Trails-making Part B test will ask participants to connect numbers (1-13) to letters (A-L) randomly written on a page. This test is scored according to accuracy and time required to make the connections (Joseph, 2013). If the participant is unable to accurately complete these tests, additional recovery time will be required. The participant's performance and disposition will be included in the documentation of study procedures performed during the visit.

Following the completion of UDS, each participant will be asked to engage in a structured interview with a study team member (see attached interview guide). The interview will be designed to assess the experience with SANO during the UDS. It is estimated that the interview will last about 15-20 minutes. The interview will be conducted in an enclosed patient room in the Surgical Specialties clinic on Shapiro 3. As explicitly stated in the informed consent, this interview will be audio recorded. Once study recruitment is completed, each interview will be transcribed and coded according to predefined thematic framework.

Finally, a chart review will be performed as a safety follow-up to capture any unanticipated ED visits, admissions, or office visits for the 7 days following the procedure. We will also record any phone calls that are made by patients within 7 days of procedure that pertain to procedure concerns.

**Management of Medical Gases Used in Study**

As the research pharmacy does not procure nor dispense gaseous inhalants, medical gases used in the study will be managed per protocol and as per BIDMC's Compressed Gas Cylinder Storage and Handling Policy #: EC-62. Nitrous and oxygen cylinders will be procured through the OR materials management specialist. The tanks for study gases will be stored in an approved gas cylinder storage rack in (Room 385) of the Shapiro Clinic for immediate usage. There is also a gas tank storage area in the Shapiro OR (close to the clinic) for additional storage. Both spaces are secured and locked off hours. Research staff will only access these supplies as necessary for the study.

## B. Statistical Considerations

**Sample Size Justification**

Based on a previous study by Jeon *et al*, the mean (SD) difference in max cystometric capacity (MCC) between repeated UDS fills was 20.6 (11.6) mL. Our sample size calculation to detect this difference between repeated fills (p less than 0.05 significance level) was 14 patients per group ($\alpha$=0.05, power=95%). We will inflate out our sample size to account for any missing data or withdrawals from the study, such that 25 patients may be enrolled. We aim to randomize 14 patients in total.

**Data Analysis**

All data will be collected and stored securely using the REDCap system. Data will be managed and analyzed by the PI and biostatistical support team at the BIDMC FIRST program. We will also be utilizing the support of outside collaborators, Dr. Scott Wang and Ranveer Vasdev for data analyses. Collaborators affiliated with outside institutions will not have access to PHI or any identifying information. They will assist with analyses based on de-identified data sent via secure electronic transfer. Upon protocol approval, a data transfer agreement will be initiated to allow for the transfer.

Primary outcome measures are patient anxiety and pain levels in the N2O group vs the oxygen only group as measured by the VAS and VAS A scores. We are specifically interested in the difference in scores between the two groups. Secondary outcome measures include the difference in several UDS parameters such as Maximum Cystometric Capacity (MCC), Pdet Max, Detrusor Leak Point Pressure (DLPP) Number of Detrusor Contractions, Maximum flow rate (QMax), and Post-void residual. These measurements will be acquired in the standard method of normal UDS. Tertiary outcome measure is operator satisfaction. In each patient group, we will utilize a custom, three question survey following each fill-void cycle to assess any difficulty with catheter placement, patient responsiveness, and patient procedural tolerance with the following options: better than expected, as expected, worse than expected.

We will also be obtaining a pre- and post-procedure State Trait Anxiety Inventory (STAI) and Pain Catastrophizing Scale (PSC) and post-procedure Situational Pain Catastrophizing Scale on all participants and compare the variation in response. Operator ease in performing the UDS will be measured by 3 simple questions assessing patient positioning and ease of catheter insertion.

Lastly, the structured interview will be analyzed according to a predefined qualitative framework to guide how our transcripts will be coded for final data analysis.

### C. Subject Selection

**Subject Population**

The study population will be all patients aged 21 to 85 years referred for UDS within the BIDMC Division of Urologic Surgery. A total of 14 patients will be enrolled for the study.

**Eligibility Criteria**

***Inclusion criteria:***

(1) Scheduled for UDS
(2) Aged 21 to 85 years
(3) No learning disabilities
(4) Suitable for nitrous oxide/oxygen IHS with willingness to undergo two UDS runs during the procedure
(5) Access to an email and computer

***Exclusion criteria:***

(1) Perioral facial hair impeding good mask seal
(2) Learning disabilities and/or inability to cognitively complete survey questions
(3) Has any of the following medical conditions:
    a. Inner ear, bariatric or eye surgery within the last 2 weeks,
    b. Current emphysematous blebs,
    c. Severe B-12 deficiency,
    d. Bleomycin chemotherapy within the past year,
    e. Heart attack within the past year,
    f. Stroke within the past year,
    g. Class III or higher heart failure.

## B4. POSSIBLE BENEFITS

We do not anticipate that subjects will directly benefit from participation. Patients receiving SANO may potentially experience decreased pain and anxiety when undergoing catheter placement.

Taking part in the study will increase scientific knowledge regarding the ability to use SANO as a means to decrease stress and anxiety for patients undergoing UDS, and still obtain similar outcomes when compared with oxygen. This may specifically benefit those patients who have prior poor experience with UDS yet need repeat studies, such as in pediatric patients.

## B5. POSSIBLE RISKS AND ANALYSIS OF RISK/BENEFIT RATIO

**Risks related to the use of questionnaires**

Minimal risks associated with the completion of questionnaires include subject fatigue and the possibility of increased anxiety in answering questions about baseline pain and pain related to the procedure. Subjects will be informed that they are free to discontinue their participation in the study at any time should they choose.

**Risks related to Nitrous Oxide administration**

Nitrous oxide is a well-known drug used in medicine for anesthetic and analgesic purposes. Its use during labor has been shown to be safe and effective, with no known long-term effects on the mother and no known effects on the infant. There are known long-term effects of environmental exposure to nitrous oxide, including infertility, when not using a scavenger system for the escaped environmental nitrous oxide. The Miniscav® nitrous waste gas evacuation pump has been FDA-approved for use in medical offices with the Nitrouseal® system. We will be using the Nitrouseal® and Miniscav® nitrous waste gas evacuation pump in the same way that has already approved by the FDA.

Nitrous oxide does have a risk of nausea and vomiting. The reported rates have been as high as 13% in literature; however, these are at higher concentration of nitrous oxide and with longer durations. The reported vomiting risk with the Nitrouseal® system is <0.5%. For the procedure, the patient is maintained in the lateral position, which should minimize any aspiration risk. Sweating, drowsiness, lightheadedness, tachycardia and facial flushing has also been reported. The patients are routinely monitored after the UDS, and any ill effects of the procedure itself or of the nitrous oxide will be assessed and cared for by our study team and clinical staff.

Approximately 5-10% of patients who undergo UDS at BIDMC exhibit dizziness or vasovagal response during the procedure. This risk is solely attributed to the nature of UDS. Due to the rapid offset of SANO (2-3 minutes), we do not believe this risk to be compounded after receipt of SANO. According to standard clinical practice, the APP performing the UDS and the SANO administrator will take special care to ensure a patient is stable and able to ambulate safely after catheter removal and completion of the UDS.

Finally, as with any inhaled gas, there can be a concern of hypoxia or apnea with administration of nitrous oxide. This event has not been routinely reported in the literature as a risk or side effect of nitrous oxide. During the procedure, patients will undergo continuous oxygen saturation and heart rate monitoring. These values will be documented in REDCap as part of the patient's study records.

If there are concerns of hypoxia, either objectively by the oxygen monitoring or subjectively by the patient, the protocol will be to immediately turn off the nitrous oxide and administer 100% oxygen until vitals return to baseline. All personnel in the room will have BLS training. The Clinical Research Center has a code cart which is readily available. e proximate to areas

**Possible Unauthorized Use of Nitrous Oxide**

Inhalation of nitrous oxide is used/abused in recreational settings with the purpose of causing euphoria and hallucinations. To prevent potential misuse, the nitrous oxide will be stored within the operating room storage area reserved for anesthetic gases during non-office hours.

**Potential for Loss of Confidentiality**

There is a potential for loss of confidentiality for participants in the study. Protections will be implemented to mitigate this risk. As detailed in our protocol, we will use REDCap to collect patient information and questionnaires. Though REDCap is generally considered secure for the purposes of PHI, it is a web-based application and the data is accessible to study team members on their own personal computers. Access to our REDCap will be limited to study team members who are trained in protecting PHI. Any electronic study files or information that is not stored on REDCap will be kept on a secure directory on the BIDMC server that is only accessible to research staff.

Only summaries of group data will be reported in any publications or presentations, and will not contain any identifying information. These precautions will protect PHI in accordance with HIPPA regulations.

**Reporting of Adverse Events**

All adverse events will be reported to the BIDMC Human Research Committee promptly in accordance with guidelines.

**Analysis of Risk/Benefit Ratio**

Based on the above risks, the principal investigator views this study as moderate risk. With the precautions and procedures to minimize risk as described in this section, we anticipate minimal complications and discomfort. In light of the study's potential benefits, the principal investigator believes the risk:benefit ratio to be favorable.

## B6. RECRUITMENT AND CONSENT PROCEDURES

**Recruitment**

The primary Urologist will introduce the SANO-UDS study to the patient at the time the UDS procedure is discussed. After the Urologist has discussed and planned for UDS, the study team will examine the list of scheduled UDS patients for the week, and a baseline examination by the clinical team for eligibility verification will be performed through a medical record review by a trained member of the research staff.
Patients who meet criteria will be reviewed by their Urology Attending who will provide authorization to contact eligible subjects. Then, patients will be sent a secure message via PatientSite (See Template Introductory Letter) to introduce the study. In addition, the patient will be called on their preferred clinical contact phone number by a study team member. The study team member will follow a templated introductory contact script (See Template Introductory Contact Script). In attempting to reach the patient, and in accordance with BIDMC Human

Research procedure, no more than ten (10) phone attempts will be performed, and all calls will take place between 10am-9pm Monday through Friday, and 10am – 5pm Saturday and Sunday. If there is no answer, study team member will leave a templated contact script (See Template No Answer Contact Script).

In the event that individuals contacted are distressed in any way by the contact, we will contact the patient's Urology Attending, who will either personally reach out to the patient to alleviate their concerns or have a designated team member reach out to the patient to alleviate their concerns.

**Consent**

Informed consent will be obtained for all participants who are potential study candidates. A qualified member of the research team will review the informed consent form with all patients who express interest in the study. The subject will be allowed to ask questions at any point. Study personnel will explain that the subject is free to refuse participation in this research study and that participation does not affect their scheduled procedure, nor their relationship with their providers at BIDMC. All patients who agree to participate will be asked to sign the ICF electronically through REDCap if they have access to a computer. Consent will be obtained before any study-specific tests or procedures are performed. If participants do not have access to email or smart device, written consent will be obtained on the day of their UDS, prior to being taken to the procedure room. Study personnel will document the consent process. Subjects will be provided with an electronic copy of the signed ICF if obtained via REDCAP electronic consent, or a copy of the print consent form.

**Subject Protection**

As subjects in the study may be patients of study investigators, measures will be taken to prevent coercion and undue influence. The study team will emphasize that participation is voluntary and will not impact their relationship with any individual at BIDMC. Investigators will be trained to conduct consent in a manner that does not lead to coercion and undue influence.

## B7. STUDY LOCATION

**Privacy**

The study will be conducted on the premises of BIDMC Longwood Campus. We will obtain lists of patients intended for UDS, and study team members will review the OMR records for inclusion and exclusion criteria. The patient will be contacted by phone either from in-office phone call or through Doximity phone application (which provides the BIDMC Urology office as the caller ID). We will ask the patient whether they are in a location that affords privacy for discussion of medical information. If they are not, we will arrange an appropriate time when the patient will have privacy for study discussion. Phone interviews by study team members will be conducted in private space to avoid the interview being overheard.

Pre-procedure questionnaires will be emailed to private patient email via the REDCap server. Data collected will be kept within the REDCap server. Access to our REDCap will only be allowed for study team members who are trained in protecting PHI.

Operator Surveys will be on paper forms with patient identifying sticker on the form. At the end of the UDS, the data will be input into the REDCap system by a study team member, and the paper version will be stored within each subject's file.

Pre-procedure and post-procedure STAI, PCS, VAS, VAS-A score, Situational Pain Catastrophizing Score (S-PCS) and Trails-making Part B tests will be obtained in a private exam room where only the patient, study team members, and clinical staff measuring vitals will be present. Questionnaire answers will be input by the patient into a tablet computer. The tablet computer will be wiped with sanitizing wipe between uses.

**Physical Location**

The UDS procedure itself will take place in the Clinical Research Center, Room ST 802 ("infusion room"). The structured interview will also take place in the Clinical Research Center, but in a different enclosed patient room than where the UDS was done. Medical record reviews will occur at a secure workstation at BIDMC or through BIDMC's VPN server.

The nitrous tanks will be stored in an approved gas cylinder storage rack in (Room ST 802) of the Clinical Research Center for immediate usage. Both spaces are secured and locked off hours.

## B8. DATA SECURITY

All OMR access and assessment will be performed on the BIDMC server using the BIDMC firewall. As detailed in our protocol, we will use REDCap to collect patient information and questionnaires. Input of PHI data into the REDCap system by team members will only be through the BIDMC server using the BIDMC firewall. Access to our REDCap will only be allowed for study team members who are trained in protecting PHI. Only summaries of group data will be reported in any publications or presentations, with no identification of individuals.

Operator Surveys will be on paper forms with patient identifying sticker on the form. At the end of the UDS, the data will be input into the REDCap system by a study team member, and the paper version will be disposed of in a disposal unit intended for medical information waste.

## B9 Multi-Site Studies

Is the BIDMC the coordinating site? ☐ Yes ☐ No

Is the BIDMC PI the lead investigator of the multi-site study? ☐ Yes ☐ No

## B10 Dissemination of Research Results

Participants will be thanked for their participation in the research study. Results of research conducted through this protocol will be published in peer-reviewed journals and presented in scientific conferences. No identifiable information will be published or presented

## References

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