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Urinary retention rates after immediate removal of Foley catheter versus backfill void trial following total laparoscopic hysterectomy: A randomized controlled trial.

Principal Investigator: Michael L. Sprague, M.D.
Faculty, Department of Gynecology Division of Minimally Invasive Gynecologic Surgery
Phone: 954-659-5565, Fax: 954-659-5560

Co-Investigators:

Primary Contact: Sara Farag, M.D.
Clinic Fellow, Minimally Invasive Gynecologic Surgery

Stephen Zimberg, M.D.
Director, Division of Minimally Invasive Gynecologic Surgery

Ben Beran, M.D.
Clinical Fellow, Minimally Invasive Gynecologic Surgery

Pamela Frazzini Padilla, M.D.
Clinical Fellow, Minimally Invasive Gynecologic Surgery

Marie Shockley, M.D.
Clinical Fellow, Minimally Invasive Gynecologic Surgery

Luz Arazo
Co-investigator, Minimally Invasive Gynecologic Surgery

INVESTIGATOR'S SIGNATURE PAGE

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The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Investigator:

Signed:

Sara Farag, M.D., MIGS Fellow	**Date:**	**6/1/17**
Michael L. Sprague, M.D.		**6/1/17**
Name Title		

Name and Address of Institution: **Cleveland Clinic Florida**
2950 Cleveland Clinic Blvd.
Weston, FL 33331

ABBREVIATIONS
(Listed alphabetically)

ACOG	*American College of Obstetrics and Gynecology*
AE	*Adverse Event*
BMI	*Body Mass Index*
CRF	*Case Report Form*
DVT	*Deep Vein Thrombosis*
IIQ-7	*Incontinence Impact Questionnaire-Short Form*
NPV	*Negative Predictive Value*
PACU	*Post-Anesthesia Care Unit*
POD	*Post-Operative Day*
PPBC	*Patient Perception of Bladder Condition*
PPV	*Positive Predictive Value*
PVR	*Post-Void Residual*
SAE	*Serious Adverse Event*
TLH	*Total Laparoscopic Hysterectomy*
UTI	*Urinary Tract Infection*

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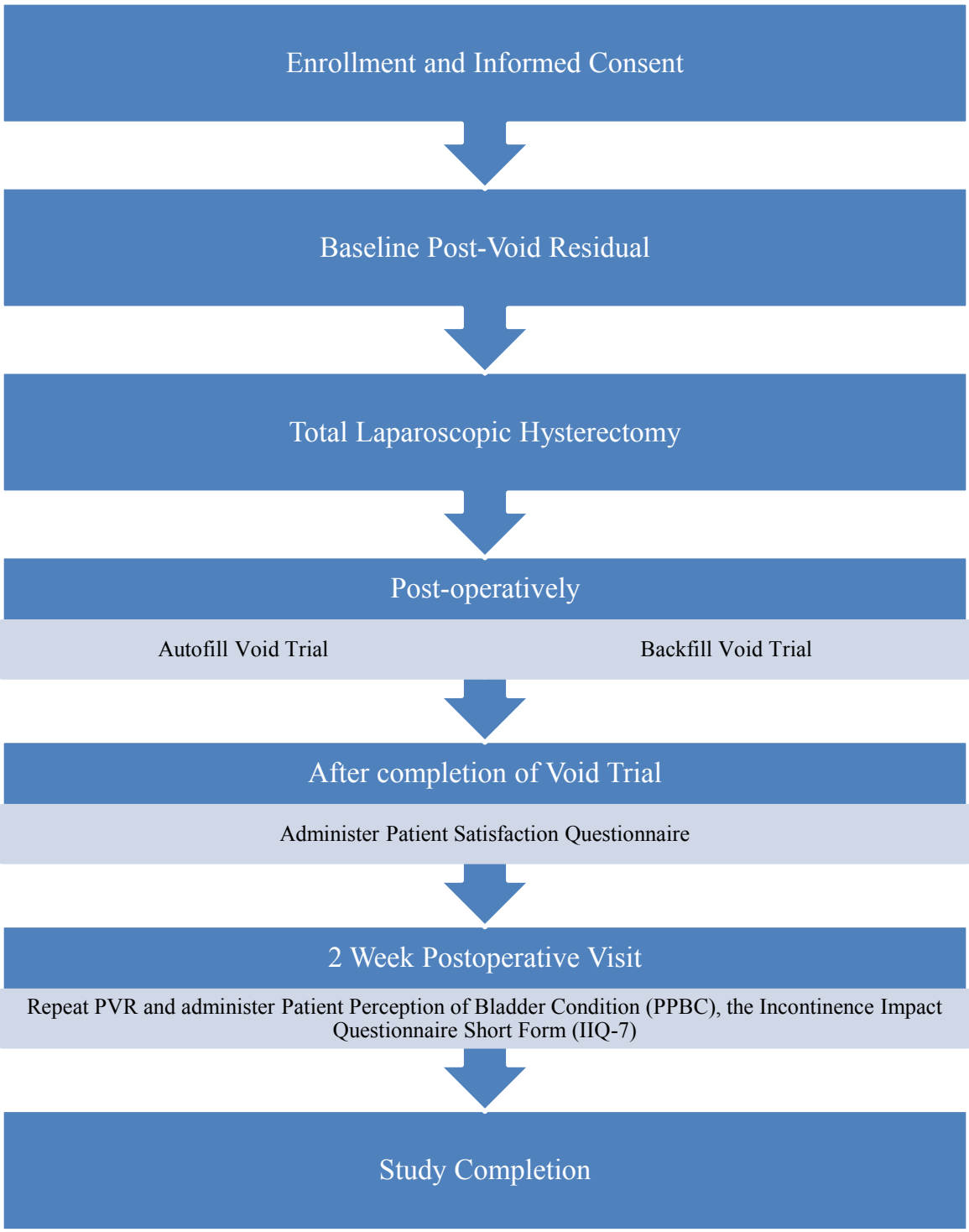
RESEARCH SCHEMA



1.0 INTRODUCTION

1.1. Background

Acute urinary retention is a complication of hysterectomies that can result in bladder over-distension and long term bladder dysfunction. The incidence of acute urinary retention after total laparoscopic hysterectomy (TLH) has been reported to be anywhere between 4% and 34%.[1-6] Studies have varied in the method of post-operative bladder challenge and the modality of hysterectomy included. Moreover, most of the published studies are retrospective chart reviews or prospective observational studies, with a lack of randomized controlled trials. Risk factors for urinary retention include type of anesthesia used, how the hysterectomy is performed, use of post-operative narcotics, pre-operative urinary retention, and possibly aggressive bladder dissection.[2,5,6] With the increased trend towards same-day discharge following TLH, urinary retention may cause unnecessary patient distress and a worsened post-operative course. Standardization of post-hysterectomy bladder challenge and identification of risk factors for urinary retention may aid in preventing urinary retention or acute bladder dysfunction.

1.2. Investigational Agents

This study does not involve investigational agents.

1.3. Prior Studies

There have been several studies published evaluating acute post-hysterectomy urinary retention and the risk factors associated with having this complication. Several of these studies are not generalizable to our patient population due to their exclusion of patients undergoing same-day discharge. Smorgick et al retrospectively evaluated urinary retention after laparoscopic total and supracervical hysterectomy as well as robotic-assisted laparoscopic hysterectomy over 9 years and found the rate of urinary retention to be 7.3% in total: 10.3% in robotic cases and 4% in laparoscopic cases. The authors concluded that the difference may be attributed to more aggressive bladder dissection in robotic cases. In this study, patients had the Foley catheters removed on post-operative day (POD) 1 as they were admitted overnight. Urinary retention was defined as inability to void by 6 hours or post-void residual (PVR) greater than 100 cc of urine.[5] In another retrospective chart review, Kandadai et al matched patients who underwent hysterectomy and had post-operative urinary retention with patients who underwent hysterectomy and did not have urinary retention in an attempt to determine if analgesic usage contributed to urinary retention. Higher post-operative narcotic doses, pre-operative usage of Tricyclic antidepressants, and pre-operative urinary retention were found to be risk factors for developing urinary retention. However, once again, these patients were admitted overnight and the Foley catheters removed on POD1. Additionally, the authors included vaginal, laparoscopic, and abdominal hysterectomies in the study.[6] Lastly, Won et al sought to report the incidence of bladder dysfunction by prospectively observing 108 women undergoing gynecologic laparoscopic surgery. The incidence of post-operative bladder dysfunction was 19.6%. This sample includes different surgeries and pathologies. Additionally, the Foley catheters were removed on POD1 and patients with same-day discharge were excluded from the study.[1]

Immediate post-operative Foley catheter removal has become more preferable since there is a nationwide effort to discharge patients undergoing laparoscopic hysterectomy on the same day of their surgeries. Additionally, early removal of Foley catheters may improve post-operative

urinary tract infection (UTI) rates. In a study performed by Liang et al comparing urinary outcomes in patients undergoing laparoscopic-assisted vaginal hysterectomy who receive a Foley catheter intra-operatively versus those who do not, 34% of patients were found to have urinary retention in the no catheter group. The patients who had an intra-operative catheter placed underwent removal on POD1 or POD2. Urinary retention occurred in 12% of those who had removal on POD1 and in 10% of those who had removal on POD2. However, the UTI rates were worsened as the Foley catheter remained in place for a longer period of time: 4% in the no catheter group, 6% in the POD1 removal group, and 18% in the POD2 removal group.[4] Ghezzi et al performed a prospective observational study of 233 women undergoing TLH or vaginal hysterectomy evaluating post-operative urinary retention after immediate Foley catheter removal. Post-op voiding dysfunction was defined as failure of voiding after surgery or PVR of 150 mL of greater. In the TLH group, 14.1% had a post-void dysfunction and 7.7% had complete urinary retention.[3] Alessandri et al later reported a prospective randomized controlled trial including vaginal, abdominal, and laparoscopic hysterectomies comparing immediate Foley catheter removal with removal of the catheter 6 hours post-operatively or 12 hours post-operatively. The urinary retention rate was 18.8% for patients in the immediate Foley catheter removal group and 0% for the other groups. However, all of the patients who had urinary retention had undergone vaginal hysterectomy under spinal anesthesia and only 15 patients in the cohort had undergone TLH.[2]

Within the Urogynecology literature, there have been several studies evaluating urinary retention after vaginal hysterectomy and other pelvic floor procedures. These studies have supported the use of a backfill technique post-operatively to prevent post-operative urinary retention. The backfill techniques involves retrograde filling of the bladder via a Foley catheter followed by allowing the patient to void and measuring the PVR. This is different from the autofill techniques which involves immediate removal of Foley catheter post-operatively then allowing the patient to void spontaneously and measuring the PVR. Foster et al randomized 55 patients to receive a backfill-assisted void trial or an autofill void trial after transvaginal surgery resulting in 38.5% of patients going home with a Foley catheter after backfill void trial versus 67.9% going home with a Foley catheter after the autofill void trial ($p = 0.02$). Additionally, patients remained in the hospital for an average of 199.5 minutes in the backfill void trial group versus 226.6 minutes in the autofill void trial group ($p = 0.08$).[7] Similarly, Geller et al randomized 60 patients undergoing urogynecologic procedures to obtaining either backfill followed by autofill void trial or autofill followed by backfill. There was a significant difference in the failure rate between the two methods with 62% failing the backfill void trial versus 84% failing the autofill void trial ($p = 0.001$). The backfill method was found to have a sensitivity of 94.4%, a specificity of 58.1%, a positive predictive value (PPV) of 56.7% and a negative predictive value (NPV) of 94.7%. On the other hand, the autofill method was found to have a sensitivity of 100%, a specificity of 25.8%, a PPV of 43.9%, and a NPV of 100%.[8] Moreover, Pulvino et al randomized 65 patients to the backfill technique or the autofill technique reporting the failure rate to be 35% in both groups but noted that there was more complete bladder emptying found in the backfill group, with a voided volume of 65% ± 0.33 and 51% ± 0.34, respectively ($p < 0.01$).

1.4. Dose Rationale and Risks/Benefits

This is not applicable as no investigational agents will be used.

1.5. Hypothesis

Failure of void trial after TLH will be lower after the backfill technique than after the autofill technique.

2.0 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective is to compare the rate of void trial failure after TLH with the backfill technique versus the autofill technique.

2.2 Secondary Objectives

The following variables will also be compared between participants undergoing backfill void trial and autofill void trial:

- Time to discharge: time from arrival to post-anesthesia care unit (PACU) to time of discharge
- Incidence of urinary retention after discharge from hospital
- Incidence of UTI in the first 2 weeks after surgery
- Participants' short term quality of life during the first 2 weeks after surgery
- Participants' satisfaction with the void trials

3.0 STUDY DESIGN

3.1 General Design

This will be a randomized control trial. Patients undergoing TLH for benign conditions will be invited and consented to participate in the study prior to the day of their surgery. Each patient will be contacted by one of the study investigators and presented with the study including the risks, benefits, and follow up requirements. She will be given the option to participate and if agrees, she will sign a consent form. All enrolled participants will have a PVR checked and recorded in the clinic using the bladder scanner that is available to us or straight catheterization. The enrolled participants will also be asked to complete the Patient Perception of Bladder Condition (PPBC) and the Incontinence Impact Questionnaire-Short Form (IIQ-7) and the completed forms will be collected by the research team (see attached "Preoperative participant questionnaire").[9,10] Each consented participant will be randomized to receive a post-operative backfill void trial or an autofill void trial on the day of her surgery. The participant will not be told of her randomization group pre-operatively; however, the surgical team will be aware of the randomization.

On the surgical day, all enrolled participants will undergo standard registration and preoperative preparation by the staff pre-operative nurse, including placement of intravenous access line and administration of standard preoperative medications. Preoperative medications (unless contraindicated due to allergy or other medication interaction) include single dose prophylactic antibiotics given prior to surgical incision, Tylenol 1,000 mg PO, Dexamethasone 10 mg IV (unless the participant has diabetes), Celebrex 200 mg PO (unless patient has a sulfa allergy, is $\geq$ 65 years old, weighs $\leq$ 50 kg, or has a CCl < 50ml/min), Ondansetron 4 mg IV, and Gabapentin 600 mg PO (300 mg PO if participant is $\geq$ 65 years old) given in the preoperative area.[11,12] Participants with a preoperative Caprini score of 5 or greater will also receive Heparin 5000 units

subcutaneously for deep vein thrombosis (DVT) prophylaxis.[13]
The participant will be taken to the operating room. Induction, intubation, and anesthesia will be administered according to standard practice by a dedicated group of anesthesia providers. Prior to surgical incision, preoperative prophylactic antibiotics will be administered. The participant will be positioned in the dorsal lithotomy position with the lower extremities in the Allen stirrups bilaterally and the bilateral upper extremities in a tucked position. Surgical sterile preparation and draping will be performed per usual technique. Vaginal antiseptic preparation will be performed with 10% Povidone-Iodine solution. A Foley catheter will be placed prior to the start of the surgical procedure. The hysterectomy will then proceed in the usual manner. After the specimen is removed from the pelvis and the vaginal cuff is closed, a cystoscopy may be performed at the discretion of each surgeon. At this time, the randomization envelope will be opened. Participants who randomize to the backfill void trial will remain with a Foley catheter in place or will have the Foley catheter replaced, in the case that a cystoscopy is performed. Patients who randomize to the autofill void trial will be given a 500 cc bolus of crystalloid by the anesthesia team prior to leaving the operating room. All skin incisions will be closed in a subcuticular fashion and sealed with skin adhesive.

The participant will emerge from anesthesia under routine monitoring and will be transferred to the PACU when meeting appropriate criteria per anesthesia discretion. A staff PACU nurse will care for the participant in the PACU administer narcotic medications as necessary and/or per participant request. Once the participants are awake and meeting criteria for discharge, the patients in the backfill group will undergo a void trial by a PACU nurse or by a doctor if the nurse is unavailable. About 300 mL of fluid will be instilled into the bladder and the Foley will then be removed. The participant will be given up to 1 hour to urinate and the amount urinated will be recorded using a commode specimen collection measurer. The PVR will be measured using a bladder scanner. If the PVR is greater than 100 mL or if the patient is unable to void within the hour, the void trial will be considered "failed" and a Foley catheter will be replaced.

The participants in the autofill void trial group will be allowed to urinate at any time within the first 3 hours after surgery. The amount urinated will be recorded using a commode specimen collection measurer. The PVR will be measured using a bladder scanner. If the PVR is greater than 100 mL, the void trial will be considered "failed" and a Foley catheter will be replaced. We anticipate that most of these patients will void spontaneously within 2 hours of arrival to the PACU. At two hours post-operatively, any patient who cannot void or does not have the urge to void will have a bladder scan. If the patient has more than 300 cc in the bladder, she will be allowed 1 more hour to void. If she cannot, a Foley catheter will be placed and she will be considered to have failed the void trial. If the patient has less than 300 cc in the bladder, another 500 cc of crystalloid bolus will be given and we will await void for another hour. At 3 hours post-operatively, these patients will undergo another bladder scan. Those with greater than 300 cc of urine in the bladder will receive a Foley catheter. Those with less than 300 cc of urine in the bladder will have a backfill void trial by placing the remaining amount of fluid into the bladder for a total volume of 300 cc. The rest of the void trial will be completed as per normal backfill void trial protocol.

The participants who have a replaced Foley catheter will receive education regarding usage of a leg bag and will be discharged home to return to the office the following business day where a

repeat void trial will be performed using the backfill method as previously outlined. If participants are unable to be discharged home, they will be admitted overnight in the hospital with documented rationale. A backfill void trial will then be performed the following day. If participants fail the 2nd void trial, a Foley catheter will be replaced and will remain in place for 1 week, at which time a backfill void trial will be repeated once again in the office. If this void trial is failed as well, participants will be educated about and asked to perform self-catheterization at home and will follow up with Urogynecology.

All participants will be discharged home with uniform medication prescriptions and instructions for usage. The medications will include Ondansetron 4mg PO every 8 hours as needed for nausea/vomiting (quantity 12), Colace 100mg PO twice daily (quantity 60), scheduled Ibuprofen 600mg PO every 6 hours (quantity 30), scheduled Acetaminophen 650mg PO every 6 hours (quantity 30), and Oxycodone 5mg PO every 4 hours as needed for breakthrough pain (quantity 30). These prescriptions are based on recent anesthesia practice guidelines.[14,15]

At the post-operative visit 10-14 days after the surgery, the participants will be evaluated and examined in the office. They will be asked to complete a questionnaire which includes the IIQ-7, the PPBC, and a void trial satisfaction question (see attached "post-operative participant questionnaire"). Participants will also be asked if they obtained a Foley catheter outside of the hospital at any urgent care centers, other doctors' offices, or emergency rooms. Additionally, participants will be asked if they have any urinary problems including dysuria, hematuria, frequency, hesitancy, urgency, or incomplete emptying. If any urinary complaints exist, participants will be asked to provide a urine sample for testing by urinalysis and urine culture. Participants will be treated per physician preference. After treatment, participation in the study will be considered completed.

3.2 Primary Study Endpoints

The primary endpoint of this study will be to determine if the rate of void trial failure after TLH is different after the autofill method versus the backfill method.

3.3 Secondary Study Endpoints

The following study endpoints will also be compared between participants undergoing backfill void trial and autofill void trial:

- The time to discharge will be measured for each participant. This will be determined by calculating the time between arrival to the PACU and the time of discharge using documentation from Epic and from the case report forms (CRFs).
- After discharge, participants will be monitored for any encounters for urinary retention (in our hospital system) and will be asked at their 10-14 day post-operative visit if they had a Foley catheter placed outside the hospital. Additionally, any participant who fails their 2nd void trial will be noted. The incidence of urinary retention post-discharge will be determined using this data.
- Any participant diagnosed with a culture-proven UTI will be noted.
- The IIQ-7 will be used to determine if there are any changes to the participants' short term quality of life before and after surgery.
- The PPBC will be used to determine if there are any changes to the participants' perception of bladder function before and after surgery.

- Participant satisfaction level with the method of void trial will be collected at the 10-14 day post-operative visit and compared between the two methods of void trial.

3.4 Primary Safety Endpoints

All intra-operative and post-operative complications will be recorded for each participant. If any adverse events are related directly to the void trial methods, these will be documented and reported to the IRB and the study will be stopped immediately for that particular participant.

4.0 SUBJECT SELECTION AND WITHDRAWAL

4.1 Inclusion Criteria

Subjects must meet the following inclusion criteria to be eligible for the study:

1. Females at least 18 years of age
2. Understand and voluntarily sign an informed consent form
3. English-speaking (able to read and understand English)
4. Undergoing robotic or laparoscopic TLH for benign indication

4.2 Exclusion Criteria

Subjects with the following exclusion criteria will not be eligible for the study:

1. Undergoing concomitant procedures in addition to hysterectomy which may cause urinary dysfunction
2. ~~Undergoing robotic-assisted laparoscopy or~~ Undergoing a laparotomy
3. Known history of pre-operative urinary incontinence or retention
4. History of prior bladder or prolapse surgery
5. Neurologic or spinal cord injury affecting bladder function
6. Pregnant women
7. Evidence of gynecologic malignancy
8. Currently taking anticholinergic medications

4.3 Subject Recruitment and Screening

Patients will be recruited from the Cleveland Clinic Florida Department of Gynecology, primarily from two providers' patients—Dr. Stephen Zimberg and Dr. Michael Sprague. These physicians will see and book patients for TLH as normally in the office. All patients scheduled for TLH will be offered enrollment in the study per the aforementioned inclusion and exclusion criteria. Enrollment will occur at the pre-operative consultation or by telephone prior to day or surgery. A brief description will be provided including the risks/benefits of enrolling in the study. An opportunity for questions will be provided. Patients who do not wish to participate in the study will not be enrolled. On the day of the surgery, in a private area of the pre-operative suite, a member of the research team will discuss the study with the patient to readdress the protocol and answer any new questions. An approved informed consent document will be signed at the pre-operative consultation if the patient is agreeable to participation. If the patient is enrolled by telephone, the informed consent document will be signed the morning of surgery.

4.4 Early Withdrawal of Subjects

Patients may withdraw from the trial at any time and for any reason. Some reasons for early withdrawal also exist. One such reason is malignancy in the final pathology report, conversion

to laparotomy, or intraoperative bladder injury requiring Foley catheter for a prolonged period of time. Early withdrawal will occur if a patient's procedure becomes more than the scheduled case only; for example, if the bowel is injured and the need to perform a bowel resection arises then the patient will be withdrawn from the study. Withdrawal from this study will not affect access to standard clinical care for post-operative visits or other gynecologic needs.

4.5 Data Collection and Follow Up for Withdrawn Subjects

If patients withdraw prior to the research intervention (backfill versus autofill void trial), they will be completely removed from the study and not followed according to the research protocol. Post-operatively, the patient's surgeon will choose the void trial method per his preference. Patients will receive routine post-operative care by their provider. If withdrawal occurs by patient preference or by meeting one of the early withdrawal criteria, the patient will be asked to follow-up according to standard of care at the 10-14 day post-operative visit. The reason for her withdrawal will be recorded. However, no further data will be collected about that patient for research purposes. If any complications arise, she will be treated appropriately.

5.0 STUDY INTERVENTION

5.1 Description

The study intervention is the performance of a backfill void trial versus an autofill void trial. These interventions are not experimental and have been described at length in the literature but not directly in our patient population.[1-5,7,8,16-21]

5.2 Treatment Regimen

The interventions were be performed post-operatively in the PACU. See the following sections for more detail as to how the study interventions will be carried out.

5.3 Method for Assigning Subjects to Study Interventions

After patients are enrolled and consented to the study, they will be randomized to receive either an autofill or backfill void trial post-hysterectomy in the PACU. The randomization process will be completed by one study personnel prior to the initiation of the study using a random number generator. The random assignment of backfill void trial or autofill void trial will be placed in envelopes prior to enrollment of the first patient. The prepared envelopes will be used in sequential order. After hysterectomy is completed and prior to the participant emerging from anesthesia, the envelope will be opened informing the surgical team which group the participant randomizes to. The study intervention will then be carried out as below.

5.4 Preparation and Administration of Study Intervention

Participants who randomize to the backfill void trial will remain with a Foley catheter in place or will have the Foley catheter replaced, in the case that a cystoscopy is performed. The participant will emerge from anesthesia under routine monitoring and will be transferred to the PACU when meeting appropriate criteria per anesthesia discretion. Once the participants are awake and meeting criteria for discharge, the patients in the backfill group will undergo a void trial by a PACU nurse or by a doctor if the nurse is unavailable. About 300 mL of fluid will be instilled into the bladder and the Foley will then be removed. The participant will be given up to 1 hour to urinate and the amount urinated will be recorded using a commode specimen collection

measurer. The PVR will be measured using a bladder scanner. If the PVR is greater than 100 mL or if the patient is unable to void within the hour, the void trial will be considered "failed" and a Foley catheter will be replaced. Patients who randomize to the autofill void trial will be given a 500 cc bolus of crystalloid by the anesthesia team prior to leaving the operating room. These participants will be allowed to urinate at any time within the first 3 hours after surgery. The amount urinated will be recorded using a commode specimen collection measurer. The PVR will be measured using a bladder scanner. If the PVR is greater than 100 mL, the void trial will be considered "failed" and a Foley catheter will be replaced. We anticipate that most of these patients will void spontaneously within 2 hours of arrival to the PACU. At two hours post-operatively, any patient who cannot void or does not have the urge to void will have a bladder scan. If the patient has more than 300 cc in the bladder, she will be allowed 1 more hour to void. If she cannot, a Foley catheter will be placed and she will be considered to have failed the void trial. If the patient has less than 300 cc in the bladder, another 500 cc of crystalloid bolus will be given and we will await void for another hour. At 3 hours post-operatively, these patients will undergo another bladder scan. Those with greater than 300 cc of urine in the bladder will receive a Foley catheter. Those with less than 300 cc of urine in the bladder will have a backfill void trial by placing the remaining amount of fluid into the bladder for a total volume of 300 cc. The rest of the void trial will be completed as per normal backfill void trial protocol. The participants who have a replaced Foley catheter will receive education regarding usage of a leg bag and will be discharged home to return to the office the following business day where a repeat void trial will be performed using the backfill method as previously outlined. If participants are unable to be discharged home, they will be admitted overnight in the hospital with documented rationale. A backfill void trial will then be performed the following day. If participants fail the 2nd void trial, a Foley catheter will be replaced and will remain in place for 1 week, at which time a backfill void trial will be repeated once again in the office. If this void trial is failed as well, participants will be educated about and asked to perform self-catheterization at home and will follow up with Urogynecology.

5.5 Subject Compliance Monitoring

Since the study interventions will both be completed by a study personnel or a trained nurse, compliance is not applicable to this study.

5.6 Prior and Concomitant Therapy

Concomitant antibiotic therapy or immunosuppressive therapy will be recorded but will not preclude the patients from being a part of the study.

5.7 Packaging

Foley catheters and leg bags are both packaged in a sterile fashion. Additionally, sterile water will be used to fill the bladder in the backfill void trials.

5.8 Blinding of Study Agent

The participants will not be blinded to the study interventions due to the nature of the void trials and their timing in relation to the participants' surgeries. Additionally, the study personnel will not be blinded to the study interventions and outcomes because they will be responsible for carrying them out and setting up follow up appointments as needed for the participants.

5.9 Receiving, Storage, Dispensing and Return

5.9.1 Receipt of Drug (Device or Treatment) Supplies

Foley catheters are used for every laparoscopic hysterectomy performed at Cleveland Clinic Florida. These are charged to the participant as part of her surgery. Void trials will not require any extra supplies outside of the scope of the surgery and all supplies are available to the nurses and study personnel in the operating rooms and PACU.

5.9.2 Storage

All necessary supplies are available in the operating rooms and in the PACU.

5.9.3 Dispensing of Study Drug (or Device)

The supplies are self-serve and can be found in the clean supply rooms of both operating rooms.

5.9.4 Return or Destruction of Study Drug (or Device)

This section is not applicable as Foley catheters are thrown away in biohazard trash cans as per routine.

6.0 STUDY PROCEDURES

6.1 Pre-registration and Screening

All patients scheduled for TLH will be offered enrollment in the study per the above inclusion and exclusion criteria. Eligibility will be confirmed at this time by a member of the research team through patient interview and review of the available electronic health record. All enrolled participants will have a PVR checked and recorded in the clinic using the bladder scanner that is available to us or straight catheterization. The enrolled participants will also be asked to complete the Patient Perception of Bladder Condition (PPBC) and the Incontinence Impact Questionnaire-Short Form (IIQ-7) and the completed forms will be collected by the research team (see attached "Preoperative participant questionnaire").[9,10]

6.2 Surgery

On the surgical day, all enrolled participants will undergo standard registration and preoperative preparation by the staff pre-operative nurse, including placement of intravenous access line and administration of standard preoperative medications. The participant will be taken to the operating room. Induction, intubation, and anesthesia will be administered according to standard practice by a dedicated group of anesthesia providers. Prior to surgical incision, preoperative prophylactic antibiotics will be administered. The participant will be positioned in the dorsal lithotomy position with the lower extremities in the Allen stirrups bilaterally and the bilateral upper extremities in a tucked position. Surgical sterile preparation and draping will be performed per usual technique. Foley catheter will be placed prior to the start of the surgical procedure. The hysterectomy will then proceed in the usual manner. After the specimen is removed from the pelvis and the vaginal cuff is closed, a cystoscopy may be performed at the discretion of each surgeon. At this time, the randomization envelope will be opened. Participants who randomize to the backfill void trial will remain with a Foley catheter in place or will have the Foley catheter replaced, in the case that a cystoscopy is performed. Those in the autofill group will have a 500

cc bolus of crystalloid prior to leaving the operating room. All skin incisions will be closed in a subcuticular fashion and sealed with skin adhesive. The participant will emerge from anesthesia under routine monitoring and will be transferred to the PACU when meeting appropriate criteria per anesthesia discretion.

6.3 Post-op Day 0 in PACU

Once the patient is awake and meeting requirements for discharge, the void trials can take place. Participants who randomize to the backfill void trial will remain with a Foley catheter in place or will have the Foley catheter replaced, in the case that a cystoscopy is performed. The participant will emerge from anesthesia under routine monitoring and will be transferred to the PACU when meeting appropriate criteria per anesthesia discretion. Once the participants are awake and meeting criteria for discharge, the patients in the backfill group will undergo a void trial by a PACU nurse or by a doctor if the nurse is unavailable. About 300 mL of fluid will be instilled into the bladder and the Foley will then be removed. The participant will be given up to 1 hour to urinate and the amount urinated will be recorded using a commode specimen collection measurer. The PVR will be measured using a bladder scanner. If the PVR is greater than 100 mL or if the patient is unable to void within the hour, the void trial will be considered "failed" and a Foley catheter will be replaced. Patients who randomize to the autofill void trial will be given a 500 cc bolus of crystalloid by the anesthesia team prior to leaving the operating room. These participants will be allowed to urinate at any time within the first 3 hours after surgery. The amount urinated will be recorded using a commode specimen collection measurer. The PVR will be measured using a bladder scanner. If the PVR is greater than 100 mL, the void trial will be considered "failed" and a Foley catheter will be replaced. We anticipate that most of these patients will void spontaneously within 2 hours of arrival to the PACU. At two hours post-operatively, any patient who cannot void or does not have the urge to void will have a bladder scan. If the patient has more than 300 cc in the bladder, she will be allowed 1 more hour to void. If she cannot, a Foley catheter will be placed and she will be considered to have failed the void trial. If the patient has less than 300 cc in the bladder, another 500 cc of crystalloid bolus will be given and we will await void for another hour. At 3 hours post-operatively, these patients will undergo another bladder scan. Those with greater than 300 cc of urine in the bladder will receive a Foley catheter. Those with less than 300 cc of urine in the bladder will have a backfill void trial by placing the remaining amount of fluid into the bladder for a total volume of 300 cc. The rest of the void trial will be completed as per normal backfill void trial protocol. The participants who have a replaced Foley catheter will receive education regarding usage of a leg bag and will be discharged home to return to the office the following business day where a repeat void trial will be performed using the backfill method as previously outlined. If participants are unable to be discharged home, they will be admitted overnight in the hospital with documented rationale. A backfill void trial will then be performed the following day. If participants fail the 2nd void trial, a Foley catheter will be replaced and will remain in place for 1 week, at which time a backfill void trial will be repeated once again in the office. If this void trial is failed as well, participants will be educated about and asked to perform self-catheterization at home and will follow up with Urogynecology.

6.4 Post-op Day 1 Visit (applicable only if 1st void trial fails)

Participants who fail the post-hysterectomy void trial (their 1st void trial) will be scheduled for a nurse visit on POD1, where a repeat void trial will be performed using the backfill method as

previously outlined. If the participant was admitted to the hospital, a backfill void trial will then be performed the following day in the hospital. If participants fail the 2nd void trial, a Foley catheter will be replaced and will remain in place for 1 week.

6.5 Post-op Week 1 Visit (applicable only if 2nd void trial fails)

Participants who fail the POD1 void trial (their 2nd void trial) will be scheduled for a nurse visit after one week, at which time a backfill void trial will be repeated once again in the office. If this void trial is failed as well, participants will be educated about and asked to perform self-catheterization at home and will follow up with Urogynecology for further management.

6.6 Post-op Week 2 Visit

At the post-operative visit 10-14 days after the surgery, the participants will be evaluated and examined in the office. They will be asked to complete a questionnaire which includes the IIQ-7, the PPBC, and a void trial satisfaction question (see attached "post-operative participant questionnaire"). Participants will also be asked if they obtained a Foley catheter outside of the hospital at any urgent care centers, other doctors' offices, or emergency rooms. Additionally, participants will be asked if they have any urinary problems including dysuria, hematuria, frequency, hesitancy, urgency, or incomplete emptying. If any urinary complaints exist, participants will be asked to provide a urine sample for testing by urinalysis and urine culture. Participants will be treated per physician preference. After treatment, participation in the study will be considered completed.

6.7 Study Calendar of Procedures

	Pre-Study	Surgery	POD0- 2 hrs post-op	POD1	Week 1	Week 2
Informed Consent	X					
Demographics	X					
Medical History	X					X
Physical/Pelvic Exam	X	X				X
PVR	X					
1st backfill versus autofill void trial with PVR			X			
2nd backfill void trial with PVR, if 1st trial failed				X		
3rd backfill void trial with PVR, if 2nd trial failed					X	
IIQ-7 Questionnaire	X					X
PPBC Questionnaire	X					X
Satisfaction Survey						X

6.8 Laboratory Procedures

No samples will be sent to the laboratory within the study.

7.0 STATISTICAL PLAN

7.1 Sample Size Determination

Due to the wide variety of incidence of voiding dysfunction found in the literature, a review of

our own cohort of patients was used to determine the sample size. From May of 2016 to April of 2017, 355 total laparoscopic benign hysterectomies were performed by the minimally invasive gynecology division. Of these, 182 had an autofill void trial and 173 had a backfill void trial. About 28.3% of the backfill void trial patients failed and went home with a catheter while 4.9% of the autofill void trial patients failed and went home with a catheter. Hence, using a 2-indendent group dichotomous power analysis with a power of 80% and a one-sided confidence interval of 95%, we will require 76 patients to be enrolled (38 patients per group). A mid-study analysis will be performed when ½ of the patients are enrolled. To account for patient dropout. We will be enrolling 10% more patients totaling 84 patients for the study.

7.2 Statistical Methods

After all data has been collected, demographic information will be compared between the two groups in order to ensure that they are similar in age, BMI, race distribution, etc. These are all assumed to be of a Gaussian distribution hence the Student's t-test will be used to compare continuous values and the Chi-Square test will be used to compare categorical values. The proportion of urinary retention will be compared using a Chi-Square test and the results from the questionnaires will also be compared, likely using a Chi-Square test for categorical values and a Wilcoxon Rank Sum test for continuous variables since the results will likely not fit a Gaussian distribution.

7.3 Subject Population(s) for Analysis

All treated patient data will be subjected to study analysis. If a patient withdraws or drops out prior to receiving a study solution, she will not be considered "treated" and will not be included in the study analysis.

8.0 SAFETY AND ADVERSE EVENTS

8.1 Definitions

An adverse event (AE) is any untoward or unfavorable medical occurrence, symptom, disease, abnormal physical exam finding, or abnormal laboratory result which occurs to a participant in research conducted by Cleveland Clinic Florida. Psychological harms also constitute adverse events.

A serious adverse event (SAE) is an adverse experience that results in any of the following outcomes:

- Death
- A life-threatening experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability / incapacity.

8.2 Recording of Adverse Events

At each contact with the subject, the investigator will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event section of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results will also be recorded in the source document. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not

the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation will be recorded and reported immediately.

8.3 Reporting of Serious Adverse Events

8.3.1 Study Sponsor Notification by Investigator (if sponsor exists)

Any serious adverse event will be reported to the IRB by the study personnel since no study sponsor exists. The following four types of events will be reported to the IRB:

1. Adverse events which are serious, unexpected, and related or possibly related to participation in the research.
2. Serious adverse events that are expected in some subjects, but are determined to be occurring at a significantly higher frequency or severity than expected.
3. Other unexpected adverse events, regardless of severity, that may alter IRB analysis of the risk versus potential benefit of the research and, as a result, warrant consideration of substantive changes in the research protocol or informed consent process/document.
4. Unanticipated Problems involving risks to subjects or others or any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB.

8.3.2 IRB Notification by Investigator

All serious adverse events will be reported to the IRB within 48 hours of occurrence. A Serious Adverse Event form will be completed by a member of the research team and faxed or emailed to the IRB. Copies of each report and documentation of communication with the IRB will be kept in the study files.

8.3.3 FDA Notification by Sponsor (if applicable)

This section is not applicable to the study.

8.4 Unblinding Procedures

This section is not applicable to the study.

8.5 Stopping Rules

An interim analysis of the patient data will be performed when 50% of the patients have completed the study. If a statistically significant proportion of patients are found to have had adverse reactions or serious adverse reactions, the study will halt. If any adverse outcome is fatal, the study will immediately halt and the IRB will be notified. In the case that the study is stopped then the IRB will be notified.

8.6 Medical Monitoring

The principal investigator and research team will oversee safety of patients throughout their participation in the study. Careful monitoring for adverse events will occur with assurance that reporting follows the above guidelines. The number and type of adverse events will be recorded in the case report forms.

9.0 DATA HANDLING AND RECORD KEEPING

9.1 Confidentiality and Privacy

All subject data will be kept in accordance with the Health Insurance Portability and Accountability Act of 1996. Only the enrollment log will contain identifiable personal health information including the patient's name and assigned research identification number. This will be kept on a secure Cleveland Clinic Florida drive, and a paper copy will be kept in a locked filing drawer in the research team's office on the Cleveland Clinic Florida property. The case report forms (CRFs) will only contain research identification numbers without protected health information. These will also be kept in a locked file. The data from the CRFs will be entered online into a RedCap database by a member of the research team. Only members of this research team will have access to this information.

9.2 Source Documents

Most of the source documents will be kept in the Epic Electronic Medical Record at Cleveland Clinic. These will include any history and physical exams, operative notes, progress notes from post-operative visits, anesthesia records, vital signs, and events related to surgery. Pertinent information will be pulled from the electronic health record onto the CRFs. The questionnaires completed by patients will be kept in a locked filing drawer in the research team's office on the Cleveland Clinic Florida property.

9.3 Case Report Forms

All CRFs will be kept in a locked drawer in the research team's office on the Cleveland Clinic Florida property. The data will be entered into a RedCap database.

9.4 Records Retention

Source documents in the electronic health record will be kept indefinitely. Paper copies of CRFs, enrollment logs, consent forms, and questionnaires will be kept in a locked filing cabinet in the research team office at Cleveland Clinic Florida for seven years.

10.0 STUDY MONITORING, AUDITING AND INSPECTING

10.1 Study Monitoring Plan

The investigator will allocate adequate time for monitoring activities by the IRB and Cleveland Clinic Florida research department. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities, and has adequate space to conduct the monitoring visit.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, government regulatory bodies, and Institutional compliance and quality assurance groups of all study related documents. The investigator will ensure the capability for inspections of applicable study-related facilities. Participation as an investigator in this study implies acceptance of potential

inspection by government regulatory authorities and applicable Institutional compliance and quality assurance offices.

11.0 ETHICAL CONSIDERATIONS

This study will be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures. This protocol and any amendments will be submitted to a properly constituted IRB, in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator before commencement of this study. All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision.

12.0 PUBLICATION PLAN

None of the results of the study carried out under this protocol will be published or passed on to any third party without the consent of the study investigators. The investigators alone hold responsibility for publication of study data and results.

13.0 REFERENCES

1 Won HR, Maley P, Chetty N, Chan K, Abbott J. Bladder dysfunction after gynecologic laparoscopic surgery for benign disease. J Minim Invasive Gynecol 2012; 19:76-80.

2 Alessandri F, Mistrangelo E, Lijoi D, Ferrero S, Ragni N. A prospective, randomized trial comparing immediate versus delayed catheter removal following hysterectomy. Acta Obstet Gynecol Scand 2006; 85:716-20.

3 Ghezzi F, Cromi A, Uccella S, Colombo G, Salvatore S, Tomera S et al. Immediate foley removal after laparoscopic and vaginal hysterectomy: Determinants of postoperative urinary retention. J Minim Invasive Gynecol 2007; 14:706-11.

4 Liang CC, Lee CL, Chang TC, Chang YL, Wang CJ, Soong YK. Postoperative urinary outcomes in catheterized and non-catheterized patients undergoing laparoscopic-assisted vaginal hysterectomy--a randomized controlled trial. Int Urogynecol J Pelvic Floor Dysfunct 2009; 20:295-300.

5 Smorgick N, DeLancey J, Patzkowsky K, Advincula A, Song A, As-Sanie S. Risk factors for postoperative urinary retention after laparoscopic and robotic hysterectomy for benign indications. Obstet Gynecol 2012; 120:581-6.

6 Kandadai P, Saini J, Patterson D, O'Dell K, Flynn M. Urinary retention after hysterectomy and postoperative analgesic use. Female Pelvic Med Reconstr Surg 2015; 21:257-62.

7 Foster RT S, Borawski KM, South MM, Weidner AC, Webster GD, Amundsen CL. A randomized, controlled trial evaluating 2 techniques of postoperative bladder testing after transvaginal surgery. Am J Obstet Gynecol 2007; 197:627.e1,627.e4.

8 Geller EJ, Hankins KJ, Parnell BA, Robinson BL, Dunivan GC. Diagnostic accuracy of retrograde and spontaneous voiding trials for postoperative voiding dysfunction: A randomized controlled trial. Obstet Gynecol 2011; 118:637-42.

9 Uebersax JS, Wyman JF, Shumaker SA, McClish DK, Fantl JA. Short forms to assess life quality and symptom distress for urinary incontinence in women: The incontinence impact questionnaire and the urogenital distress inventory. continence program for women research group. Neurourol Urodyn 1995; 14:131-9.

10 Coyne KS, Matza LS, Kopp Z, Abrams P. The validation of the patient perception of bladder condition (PPBC): A single-item global measure for patients with overactive bladder. Eur Urol 2006; 49:1079-86.

11 Nelson G, Altman AD, Nick A, Meyer LA, Ramirez PT, Achtari C et al. Guidelines for pre- and intra-operative care in gynecologic/oncology surgery: Enhanced recovery after surgery (ERAS(R)) society recommendations--part I. Gynecol Oncol 2016; 140:313-22.

12 Modesitt SC, Sarosiek BM, Trowbridge ER, Redick DL, Shah PM, Thiele RH et al. Enhanced recovery implementation in major gynecologic surgeries: Effect of care standardization. Obstet Gynecol 2016; 128:457-66.

13 Caprini JA. Individual risk assessment is the best strategy for thromboembolic prophylaxis. Dis Mon 2010; 56:552-9.

14 Chou R, Gordon DB, de Leon-Casasola OA, Rosenberg JM, Bickler S, Brennan T et al. Management of postoperative pain: A clinical practice guideline from the american pain society, the american society of regional anesthesia and pain medicine, and the american society of anesthesiologists' committee on regional anesthesia, executive committee, and administrative council. J Pain 2016; 17:131-57.

15 Urbach DR, Harnish JL, McIlroy JH, Streiner DL. A measure of quality of life after abdominal surgery. Qual Life Res 2006; 15:1053-61.

16 Boccola MA, Sharma A, Taylor C, Wong LM, Travis D, Chan S. The infusion method trial of void vs standard catheter removal in the outpatient setting: A prospective randomized trial. BJU Int 2011; 107 Suppl 3:43-6.

17 Du J, Marshall D, Leyland J, Shaw L, Broome KE, Mason DF. Prospective, multicentre, randomized controlled trial of bladder filling prior to trial of void on the timing of discharge. ANZ J Surg 2013; 83:239-42.

18 Odom BD, Ehlert M, Gupta P, Cholyway R, Boura JA, Killinger KA et al. Clinical comparison of 2 trial-of-void methods after outpatient midurethral sling placement. Female Pelvic Med Reconstr Surg 2016; 22:172-4.

19 Pulvino JQ, Duecy EE, Buchsbaum GM, Flynn MK. Comparison of 2 techniques to predict voiding efficiency after inpatient urogynecologic surgery. J Urol 2010; 184:1408-12.

20 Tunitsky-Bitton E, Murphy A, Barber MD, Goldman HB, Vasavada S, Jelovsek JE. Assessment of voiding after sling: A randomized trial of 2 methods of postoperative catheter management after midurethral sling surgery for stress urinary incontinence in women. Am J Obstet Gynecol 2015; 212:597.e1,597.e9.

21 Turner LC, Kantartzis K, Shepherd JP. Predictors of postoperative acute urinary retention in women undergoing minimally invasive sacral colpopexy. Female Pelvic Med Reconstr Surg 2015; 21:39-42.

14.0 ATTACHMENTS

- Feasibility Checklist
- Sample Consent Form
- Case Report Form
- Post-Operative Participant Questionnaire
- Post-Operative Participant Questionnaire