Better Lithotripsy and Ureteroscopy Evaluation of Stenting (BLUES):
A pragmatic randomized multi-center comparative effectiveness study of silicone vs non-silicone stents for ureteroscopy in patients with kidney stone disease

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Study Intervention: Usual urological care of insertion of ureteral stent at the end of ureteroscopy for stone disease. Study arms will consist of either Coloplast Imajin Hydro ureteral stent vs. non-silicone Polyurethrane/Percuflex ureteral stent (any manufacturer).

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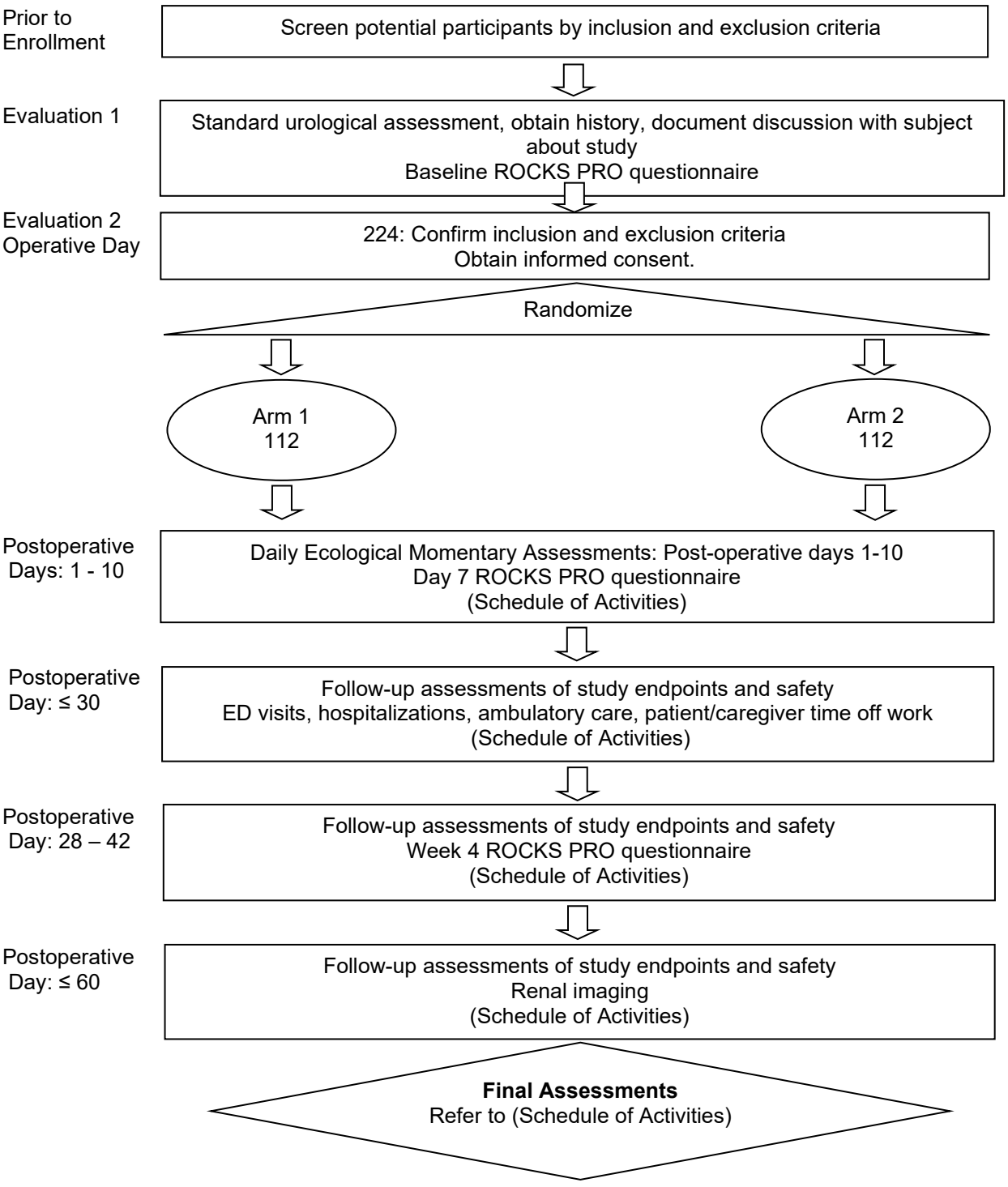
ABBREVIATIONS

AE	Adverse Event
AUA	American Urological Association
BCBSM	Blue Cross Blue Shield of Michigan
BLUES	Better Lithotripsy and Ureteroscopy Evaluation of Stenting
CFR	Code of Federal Regulations
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CRF	Case Report Form
DCC	Data Coordinating Center
DOOR	Desirability Of Outcome Ranking
DSMC	Data Safety Monitoring Committee
ED	Emergency Department
EMA	Ecological Momentary Assessments
FDA	Food and Drug Administration
HRQoL	Health Related Quality of Life
ICH GCP	International Conference on Harmonisation Good Clinical Practice
ICIQ-S	International Consultation on Incontinence Questionnaire - Satisfaction
ICU	Intensive Care Unit
IRB	Institutional Review Board
LURN SI-10	Lower Urinary Tract Dysfunction Research Network Symptom Index
LUTS	Lower Urinary Tract Symptoms
m-ITT	Modified Intent-to-Treat
MUSIC	Michigan Urological Surgery Improvement Collaborative
NIH	National Institutes of Health
PI	Primary Investigator
PRO	Patient Reported Outcome
PROMIS®	Patient-Reported Outcomes Measurement Information System
QI	Quality Improvement
RCT	Randomized Controlled Trial
ROCKS	Reducing Operative Complications from Kidney Surgery
SAE	Serious Adverse Event
SoA	Schedule of Activities
U-CTO	Urology Clinical Trials Office
URS	Ureteroscopy
US	United States
USSQ	Ureteral Stent Symptom Questionnaire

Section 1: STUDY SCHEMA



Section 2: STUDY SYNOPSIS

Title:	Better Lithotripsy and Ureteroscopy Evaluation of Stenting (BLUES) in Michigan Urological Surgery Improvement Collaborative (MUSIC)
Study Description:	Multi-center pragmatic randomized comparative effectiveness study of ureteral stent composition for ureteroscopy in patients with kidney stone disease. We hypothesize that a ureteral stent made of silicone, will have superior outcomes when compared to non-silicone stents.
Objectives:	Primary objective: • To assess health-related quality of life in patients with urinary stone disease stented with silicone or non-silicone ureteral stents at ureteroscopy Secondary objectives: • To compare 30-day emergency department visits and hospitalization rates between study arms • To compare rates and intensity of ambulatory healthcare encounters after ureteroscopy and stenting between study arms • To compare stone-free rates between study arms • To compare abnormal imaging findings after ureteroscopy and stenting between study arms

Endpoints:	Primary Endpoint:
	• PROMIS® scores of pain intensity and pain interference at 7 days
	Secondary Endpoints:
	• PROMIS® scores of pain intensity and interference at 4 weeks
	• NIH LURN SI-10 scores at 7 days
	• NIH LURN SI-10 scores at 4 weeks
	• Composite healthcare utilization metric within 30 days
	  ○ Hospitalization and ICU care
	  ○ Unplanned hospitalization
	  ○ Emergency department visit
	  ○ Ambulatory encounter: Clinic visit
	  ○ Ambulatory encounter: Phone call or message
	• Abnormal imaging findings within 60 days
	• Stone-free rates within 60 days
	Exploratory Endpoints:
	• Number of days taken off work by patient
	• Number of days taken off work by caregiver
	• Ecological Momentary Assessments (EMA) measured via daily text message for 10 days
	  ○ Daily visual analog scale pain survey score
	  ○ PROMIS® daily ability to participate in social roles and activities score
	• Composite score difference between Winratio and Desirability Of Outcome Ranking (DOOR)
	• Number of patients receiving opioid prescriptions
	• ICIQ-S Treatment Satisfaction scores at 7 days
	• ICIQ-S Treatment Satisfaction scores at 4 weeks

Study Population:	224 patients, any gender, age ≥18 years, in the State of Michigan
Phase:	Not applicable
Description of Sites/Facilities Enrolling Participants:	Multi-center study of 6 urology practices within the Michigan Urological Surgery Improvement Collaborative (MUSIC) with University of Michigan as the coordinating center.
Description of Study Intervention:	*Insertion of ureteral stent at the end of ureteroscopy for stone disease.* Study arms will consist of either silicone (Coloplast Imajin Hydro) ureteral

	stent vs. non-silicone (Polyurethrane/Percuflex) ureteral stent (any manufacturer).
Study Duration:	30 months (3 months pre-enrollment and set up; 24 months patient enrollment; 3 months study close and analysis).
Participant Duration:	2 months

Section 3: STATEMENT OF COMPLIANCE

The study will be carried out in accordance with United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or 21 CFR Part 812)

The funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight have completed Human Subjects Protection Training.

The protocol, informed consent form(s), and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

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Section 4: STUDY BACKGROUND AND RATIONALE

Section 4.1: Study Environment

The Michigan Urological Surgery Improvement Collaborative (MUSIC) is a physician-led quality collaborative comprised of a consortium of urology practices. The collaborative is designed to evaluate and improve the quality and cost-efficiency of urological care in the state of Michigan. The collective benefits of this effort will extend to providers, healthcare systems, and most importantly, patients with urologic conditions including prostate cancer, kidney stones and small renal mass diagnoses. The MUSIC vision is to be an innovator in physician-led quality improvement (QI) activities related to the care for patients with urologic diseases. By collecting clinically-relevant data, comparing performance among peers, sharing best practices, and implementing changes in clinical behavior we will achieve more efficient utilization of healthcare resources, improve care delivery in our own environments, and enhance the quality, value, and treatment outcomes for men and women in Michigan with various urologic diseases. Part of MUSIC, the Reducing Operative Complications from Kidney Stones (ROCKS) initiative aims to improve the quality of care specifically for patients with kidney stones. One of the primary objectives of ROCKS is to reduce modifiable Emergency Department (ED) visits following commonly performed kidney stone surgeries such as ureteroscopy and shockwave lithotripsy. Started in 2016, ROCKS has made significant efforts to improve multiple aspects of the surgical journey for patients with kidney stones.

ROCKS PRO is a QI initiative that allows urologists in Michigan to better understand the patient experience following kidney stone surgery. This allows development of enhanced recovery pathways for patients undergoing kidney stone surgery with the hope to improve overall patient care across the state.

ROCKS PRO utilizes questions from several validated PRO questionnaires. These include the Patient-Reported Outcomes Measurement Information System (PROMIS®), a validated instrument developed by the National Institutes of Health to assess pain and bother in patients. It consists of questions regarding the patients' health-related symptoms of function and pain management (pain intensity and interference). ROCKS PRO also utilizes questions from the Lower Urinary Tract Dysfunction Research Network (LURN)-Symptom Index (LURN SI-10) questionnaire, the International Consultation on Incontinence Questionnaire (ICIQ)-Satisfaction (ICIQ-S), two questions regarding time off work for themselves and their caregiver, and one additional question asked to address ureteral stent specific regret taken from the Ureteral Stent Symptom Questionnaire. The LURN SI-10 assesses urinary frequency, nocturia, urgency, incontinence, bladder pain and voiding. ICIQ-S is a validated questionnaire that assesses aspects of experience, expectations, and outcomes to evaluate satisfaction after surgery. (Figure 1)

The aims of ROCKS PRO are as follows:

- Improve patient outcomes following ureteroscopy and shockwave lithotripsy through data collection, performance feedback, and sharing of best practices.
- Develop ways to improve post-operative outcomes through the collection and analysis of PRO surveys for MUSIC patients by tracking their recovery after undergoing kidney stone surgery.

Section 4.2: Epidemiology

Nephrolithiasis (kidney stone disease) affects 1 in 10 people in the United States.(1) 10.9% of patients with nephrolithiasis undergo ureteroscopy (URS) for treatment.(1) URS, is a relatively quick procedure, performed mainly at ambulatory centers, where a semi-rigid or flexible endoscope is inserted into the ureter or kidney via the urethra to treat urinary stones. Recent data demonstrates that URS is the most common surgical therapy for nephrolithiasis,(2, 3) and it is estimated that over 500,000 procedures are performed annually in this country.(4) Following URS for nephrolithiasis, ureteral stents are commonly placed for a temporary period of time permitting drainage of urine from the kidney. In the state of Michigan, 73% of urologists place a ureteral stent after URS with surgeon variation ranging from 10 to 100%.(5) While routinely used, ureteral stents are associated with patient morbidity that includes pain, urinary discomfort, unplanned ED visits, and hospitalization.(5) Prior work has demonstrated that stent morbidity can result in patient suffering, lost economic revenue due to work incapacity, and an increase in healthcare costs due to unplanned healthcare utilization.(6) Patients with ureteral stents after URS have been shown to consume significant healthcare recourses especially in the ambulatory care environment,

where nurses and doctors have to deal with enquiries of patient pain, prescribing medication, and unplanned office visits.(7)

Section 4.3: Current Practice
A ureteral stent is a flexible, small, hollow tube measuring 24-30 cm in length that sits between the bladder and kidney, and permits drainage of urine from the kidney. Ureteral stents are FDA approved devices and widely available as guideline recommended care for ureteroscopy. Stents are designed and utilized to avoid adverse events and unplanned operations after URS such as for urinary obstruction or sepsis.(8) Stent placement is recommended after URS in many clinical scenarios for a temporary period of time permitting drainage of urine from the kidney. There are specific indications for stent use, and not all patients require it. American Urological Association (AUA) guidelines recommend stent placement for patients undergoing ureteroscopy with ureteric injury, evidence of ureteral obstruction, a large stone burden (>1.5 cm), a solitary kidney, renal functional impairment, and in those in whom another ipsilateral procedure is planned.(8) Urologists report placing ureteral stents routinely in approximately 80% of all cases.(9) The risks of stents include: infection, encrustation, obstruction, rupture, migration, bladder irritation symptoms, pain, hematuria, erosion. Following placement, the stent is often removed 1-3 weeks later by the urologist in the office.

In MUSIC, we recently performed an extensive RAND/UCLA Appropriateness Method process involving 15 diverse urologists across Michigan to define uncomplicated URS in real-world practice and provide information on clinical scenarios appropriate for stent omission (Appendix 1). During this process it was clear that very few urologists would consider stent omission for larger stones (i.e. stones 1-1.5 cm in size) regardless of its location (renal or ureteral) (dark red bars in Appendix 1), or even for smaller stones, if a device during surgery called the ureteral access sheath (UAS), was used (light red bars in Appendix 1). The UAS is used in 37% of URS cases in Michigan.(10) We also learned from this process that many urologists would opt for stent omission if the patient was pre-stented, i.e. having a stent already in place at the time of surgery because it was placed as an emergency in patients with ureteral colic and obstruction. This process in MUSIC has provided us real-world information that allowed us to design a clinical study with appropriate inclusion criteria that can optimally assess the benefits of ureteral stenting in clinical practice.

Section 4.4: Justification
Stents themselves are associated with significant patient morbidity that includes pain, blood in the urine, lower urinary tract symptoms (LUTS) and urinary discomfort which can result in an ED visit for evaluation, and sometimes hospitalization because of infection.(5) There has been great interest in the role of silicone as an alternative stent material due to the potential for decreased patient morbidity and encrustation.(11, 12) Bacterial biofilm formation and mineral deposition (encrustation) lead to ureteral wall inflammation, trauma and pain. Prospective clinical studies comparing the use and outcomes of non-silicone stents versus silicone stents is limited, but has demonstrated improvements in stent related morbidity and pain.(12, 13) To date, there have been no studies examining outcomes of silicone ureteral stent placement in the US healthcare system using validated and patient friendly PRO measures, that also assess the downstream consequences of healthcare resources including ambulatory nursing/physician care utilization and unplanned healthcare encounters such as ED visits. Therefore, we propose a comparative effectiveness study to assess outcomes of a standard non-silicone ureteral stent versus silicone ureteral stent placement after URS to understand differences in patient health-related quality of life, morbidity, and its consequences for patients and their caregivers. The pragmatic study design will encourage patient and urologist participation and reduce resource use. Our proposed study will be the first to evaluate the Imajin silicone stent in the United States healthcare system. MUSIC has become an international leader in urological quality improvement and is uniquely situated to provide practical real-world evidence that has the potential to change practice.

No more than minimal increased risk to the participants is expected for the present study. All potential participants are planning to undergo a surgical procedure (URS) with a board-certified urologist trained in URS with stent placement in accordance with AUA guidelines. They will be placing either a non-silicone (standard) ureteral stent or a silicone ureteral stent, both of which are FDA approved.(14, 15) Neither the stent, study protocol, nor manual of operation requires alteration to standard of care.

Section 4.5: Potential Benefits

Immediate. Based upon prior RCT outside of the United States, the use of silicone ureteral stents has the potential to decrease pain and LUTS after URS.(12) Decreased pain and LUTS after URS secondarily could decrease the rate of ambulatory healthcare utilization, opioid prescriptions, postoperative ED visits, and unplanned hospitalizations. It could also decrease the number of days required to miss work due to recovery.

Long-range. Decreased pain and LUTS after URS secondarily could decrease a patient's exposure to opioid analgesia postoperatively. Less patient requirements for opioid analgesia could decrease the incidence of new persistent long-term use of opiates in these patients.

Section 5: STUDY OBJECTIVES

Section 5.1: Primary Objectives

1. To determine the health-related quality of life and symptoms in patients with urinary stone disease stented with silicone or polyurethane stents at ureteroscopy.

Section 5.2: Secondary Objectives

1. To compare 30-day emergency department visits and hospitalization rates between study arms
2. To compare rates and intensity of ambulatory healthcare encounters after ureteroscopy and stenting between study arms
3. To compare stone-free rates between study arms
4. To compare abnormal imaging findings after ureteroscopy and stenting between study arms

Section 5.3: Exploratory Objectives

1. To compare days taken off work by patient between study arms
2. To compare days taken off work by caregiver between study arms
3. To compare Ecological Momentary Assessments (EMA) measured via daily text message for 10 days between study arms
4. To compare Composite score difference between Winratio and Desirability Of Outcome Ranking (DOOR) between study arms
5. To compare number of patients receiving opioid prescriptions between study arms
6. To compare ICIQ-s score at 7 days between study arms
7. To compare ICIQ-s score at 4 weeks between study arms

Section 5.4: Endpoints

- Primary Efficacy Endpoint(s):
    - Silicone stent placement will be associated with significantly improved PROMIS® scores of pain intensity and interference at 7 days compared to non-silicone stent placement.
- Secondary Efficacy Endpoint(s):
    - Silicone stent placement will be associated with equivalent PROMIS® scores of pain intensity and interference at 4 weeks compared to non-silicone stent placement.
    - Silicone stent placement will be associated with significantly improved NIH LURN SI-10 scores from baseline at 7 days compared to non-silicone stent placement.

- Silicone stent placement will be associated with equivalent difference in NIH LURN SI-10 scores from baseline at 4 weeks compared to non-silicone stent placement.
- Silicone stent placement will be associated with improved composite healthcare utilization metric within 30 days compared to non-silicone stent placement.
  - Hospitalization and ICU care
  - Unplanned hospitalization
  - Emergency department visit
  - Ambulatory encounter: Clinic visit
  - Ambulatory encounter: Phone call or EMR message
- Silicone stent placement will be associated with equivalent abnormal imaging findings within 60 days compared to non-silicone stent placement.
  - New/worsening hydronephrosis
- Silicone stent placement will be associated with equivalent stone-free rates within 60 days compared to non-silicone stent placement.

- Tertiary/Exploratory Endpoints(s):
  - Silicone stent placement will be associated with significantly improved Ecological Momentary Assessment (EMA) scores measured via daily text message for 10 days compared to non-silicone stent placement.
    - Daily visual analog scale survey for pain
    - PROMIS® daily ability to participate in social roles and activities score
  - Silicone stent placement will be associated with significantly less number of days taken off work by patient.
  - Silicone stent placement will be associated with significantly less number of days taken off work by caregiver.
  - Silicone stent placement will be associated with significantly improved composite healthcare utilization metric within 30 days compared to non-silicone stent placement using Desirability of Outcome Rating (DOOR) method
    - The WinRatio and DOOR composite healthcare utilization metric ratios' sizes and directions will be compared.
  - Silicone stent placement will be associated with significantly less number of opioid prescriptions received.
  - Silicone stent placement will be associated with significantly improved ICIQ-S scores at 7 days compared to non-silicone stent placement.
  - Silicone stent placement will be associated with significantly improved ICIQ-S scores at 4 weeks compared to non-silicone stent placement.

Section 6: PATIENT ELIGIBILITY

The Michigan Urological Surgery Improvement Collaborative (MUSIC) is a Michigan-based, physician-lead quality collaborative comprised of a consortium of urology practices. The collaborative is designed to evaluate and significantly improve the quality and cost efficiency of urologic care in the state of Michigan. The participating sites submit data to the MUSIC clinical registry maintained by the MUSIC Coordinating Center and attend tri-annual consortium-wide meetings each year to compare performance, share best practices, and ultimately implement changes in clinical behavior. The consortium is funded by Blue Cross Blue Shield of Michigan (BCBSM) and the program activities are managed by the MUSIC Coordinating Center, which is housed at the University of Michigan.

ROCKS is a QI initiative within MUSIC to measure the frequency of ED visits following ureteroscopy.

Eligible BLUES patients include those that are enrolled in MUSIC ROCKS and ROCKS PRO and $\geq$18 years of age with a kidney or ureteral stone and are planned to have a ureteroscopy where stent placement is planned. Based on inclusion and exclusion criteria these patients will be identified in the clinic by MUSIC urologists at practices participating in BLUES.

Subjects must meet all of the inclusion and exclusion criteria to be enrolled to the study. Study treatment may not begin until a subject is enrolled.

Section 6.1: Inclusion Criteria
In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Male or female, aged ≥18 years
4. Planned treatment of unilateral renal and/or ureteral stones, largest stone ≤ 2.0 cm in size measured on abdominal x-ray, Ultrasound or CT scan.
    i. Renal stone defined as only renal location of stone(s).
    ii. Ureteral stone defined as ureteral only or ureteral and renal stone(s).
5. Planned unilateral ureteroscopy with stent placement without stent string.
6. Ability to take oral medication.
7. Ability and willingness to complete and adhere to survey questions and responses throughout study duration.

Section 6.2: Exclusion Criteria
An individual who meets any of the following criteria will be excluded from participation in this study:

1. Known planned secondary or staged procedure
2. Presence of anatomical anomalies (e.g. solitary, horseshoe, fused crossed ectopia, pelvic kidney)
3. Presence of any prior urinary diversion (e.g. ileal conduit, orthotopic neobladder)
4. Presence of any indwelling ureteral stent prior to ureteroscopy
5. Presence of any indwelling nephrostomy tube prior to ureteroscopy
6. Ancillary ureteroscopy to treat residual fragments in the 3 months after percutaneous renal stone surgery.
7. Renal stone located in diverticulum
8. No indication for stent placement (e.g. spontaneous passage)
9. Bladder stone location
10. Pregnancy or lactation
11. Known allergic reactions to polyurethane or silicone

Section 7: SUBJECT SCREENING AND REGISTRATION PROCEDURES
Subjects will be recruited from predesignated MUSIC Urology clinics at participating institutions/sites.

Participating MUSIC Urologists will evaluate patients in their clinical practice for study inclusion or exclusion criteria. Preoperative evaluation, labs and imaging studies will be evaluated per the standard practice of the participating urologist based off best practice recommendations. It is the responsibility of the local site investigator/delegate to determine patient eligibility. If the urologist identifies their patient as a potential participant, the study will be discussed with them at their evaluation. The BLUES study brochure may also be given to the potential participant. If the subject expresses an interest, the urologist or local site delegate will contact the BLUES study team with the patient contact information and stone location (renal only or ureteral). The BLUES study team consists of the MUSIC ROCKS program manager, statistician, BLUES study coordinator(s), study principal investigator, and study co-investigator.

Enrollment in BLUES is voluntary. If a patient does agree to participate in BLUES, they will be enrolled prior to undergoing ureteroscopy and stent placement. The patient will undergo surgical consent for ureteroscopy and stenting per the routine clinical care process. Patients who agree to take part in the BLUES study will have their name, contact, and other clinical information relevant to their upcoming ureteroscopy and stent placement entered into the MUSIC registry.

Prospective study participants may be consented by the BLUES study coordinator, other BLUES study team member, the site principal investigators, or other site employees trained and approved to conduct study related activities per local IRB policies. The individual performing the consenting process will

educate the patient on the study and protocol by phone, video communication, or in person. If the potential participant continues to express interest in participation, study materials and consent will be provided to the patient via an E-consenting platform compliant with 21 CFR 11, such as SignNow or REDCap. Paper consent forms using handwritten signatures may also be used in lieu of E-consenting. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The individual conducting the consenting will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants will have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate.

The participant will sign the informed consent document prior to any procedures being done specifically for the study. The ROCKS PRO baseline questionnaire is being completed as a part of ROCKS PRO program prior to consent being obtained for the BLUES trial. The data received from the ROCKS PRO baseline questionnaire will not be part of this research prior to signing BLUES consent. The standard urological assessment is not a component of this research, rather, it is conducted simply as a part of a urologists clinical practice ahead of a procedure. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

The BLUES study coordinator, another member of the BLUES study team, or a local site designee will register the patient with Arbormetrix for the ROCKS BLUES clinical registry and ROCKS PRO. As part of the subject enrollment process, data collection will include all MUSIC, MUSIC ROCKS and ROCKS PRO data. If a local performance site designee performs the registration, a member of the BLUES study team will review the submitted registration information for accuracy. In addition, a copy of the completed Eligibility Worksheet signed and dated by the site investigator or designee will be sent back to the BLUES study coordinator.

The individual performing the consenting and/or members of the BLUES study team will be available for any further counseling the patient requires to ensure that all questions are answered and to ensure that the patient is interested in participation.

Participants at a given performance site who meet all inclusion/exclusion criteria will be randomized using Randomize.net or a similar randomization methodology as endorsed by the Michigan Institute for Clinical & Health Research (MICHR). Subjects will be randomized to either silicone or non-silicone ureteral stent placement at a 1:1 allocation ratio. Blocked, stratified randomization based upon surgeon classified stone location (renal only versus ureteral), with random block sizes will be used to ensure group balance. Randomization list will be determined separately in strata defined by state the stratification factor/s here. The randomization code will be generated by an independent statistician.

At the time of surgery, if baseline PRO has been completed, prior to placement of the stent, the surgeon will be notified via email/text message and the surgeons operating room staff can reference the MUSIC registry to confirm if the patient should have a silicone vs non-silicone stent based on random allocation by the BLUES study coordinator or another member of the BLUES study team. Only patients who are randomized, remain eligible prior to stent placement, and receive the study treatment will be counted towards the treatment population of 224 participants. These patients will receive PRO questionnaires, via the ROCKS PRO infrastructure, pre-operatively and at 7 days, and 4 weeks after surgery. If the patient is unable to complete the PRO questionnaires through the ROCKS PRO infrastructure, the patient may complete an email survey via REDCap, survey by phone from a BLUES study team member, or paper questionnaires. Patients will also receive text messages which include pain-specific questionnaires to be completed daily for 10 days after surgery. The process of completing the ROCKS PRO questionnaire is

the same, regardless of the patient's participation in the BLUES study. A patient can withdraw or decline participation in BLUES and/or ROCKS PRO at any time.

Section 8: TREATMENT PLAN
Section 8.1: Treatment overview
Participating BLUES practices will utilize the MUSIC Registry and ROCKS PRO as a tool to enroll and collect patient surveys. Through ROCKS PRO, patients are provided via email a secure and unique link to the MUSIC Registry patient portal. An electronic introduction for ROCKS PRO will then be presented. Patients will not be required to participate and may choose to be removed from future correspondence by emailing or calling the MUSIC Coordinating Center directly.

If participating, they will be directed to the baseline questionnaire consisting of questions regarding health-related symptoms, functions and pain management before undergoing ureteroscopy. Automated email survey links will be sent to patients to complete ROCKS PRO questionnaires pre-operatively and at 7 days, and 4 weeks after surgery (Figure 1). Patients with cell phone numbers who agree to participate in BLUES will be asked to complete EMA of pain via a visual analog scale score and one question from the PROMIS® Ability to Participate in Social Roles and Activities Questionnaire (Figure 2), for 10 days after surgery.

If a patient does not log-in or fails to complete the baseline survey, they will receive an electronic automated reminder and will be contacted by the MUSIC Coordinating Center. If a patient does not log-in or fails to complete the 7-day survey, they will receive an electronic automated reminder and will be contacted by the MUSIC Coordinating Center on day 8 and 9, to facilitate its completion by the end of post-operative day 10. The BLUES Study Team may also administer the PRO questionnaires via REDCap, phone, or paper if the participant is unable to complete suveys through the MUSIC Registry.

Figure 3 depicts the timeline and flow chart of the recruitment and follow-up process. If it is past the patient's operative date they will not be enrolled or contacted.

The patient's surgery will proceed per standard of care, and their follow up, imaging and clinic visits will be directed by the local surgeon according to their local protocol. The BLUES study is pragmatic. Stents will be removed at a time and duration per the surgeon's discretion. The patient's information regarding post-operative course will be collected into the registry 60 days after the surgery, keeping with current practice for MUSIC ROCKS patient registry entry.

Section 8.2: Operative
It is not anticipated that either arm will be associated with adverse events above and beyond what is experienced normally with these therapies. No more than minimal increased risk to the participants is expected for the present study. All potential participants are planning to undergo a surgical procedure (URS) with a board-certified urologist trained in URS with stent placement in accordance with AUA guidelines. They will be placing either a non-silicone (standard) ureteral stent or a silicone ureteral stent, both of which are FDA approved. All of which is considered usual care.

At the end of ureteroscopic procedure, a ureteral stent will be placed by the urologist in the standard fashion that each urologist is trained to perform. Stent sizing, technique, duration and removal technique will be determined by the individual urologist and their standard practice.

Patients randomized to the silicone stent cohort will utilize the Coloplast Imajin Hydro (Silicone Hydro-Coated Double Loop Ureteral Stent)

- This stent is commercially available and is being used in accordance with approved labeling: "The Silicone Hydro-Coated Double Loop Ureteral Stents are used for:
    - Drainage of the upper urinary tract over fistulas or ureteral obstacles
    - Healing of the ureter"
- Stent sizes
    - 6fr x 24

- 6fr x 26
- 6fr x 28

Patients randomized to the non-silicone stent cohort will utilize any commercially available non-silicone ureteral stent for its approved indication. The stents denoted below are commonly used non-silicone stents and are not individually compared against the object of the study (Imajin Hydro silicone stent above).

- Device model(s)
  - Boston Scientific
    - Percuflex™
    - HYDROGEL COATED Percuflex Plus™
    - Contour™
  - Becton Dickinson (Bard)
    - Bard double pigtail soft polyurethane
  - Cook
    - Sof-Flex double loop polyurethane
- Stent size(s)
  - 6fr x 24
  - 6fr x 26
  - 6fr x 28

Specific assessments obtained on the operative day, include:

- Ureteral stent characteristics
  - The ureteral stents in the comparative effectiveness study are FDA approved commercially available devices that will be utilized by the urologists. Urologists will be trained and educated on documenting the specific size, brand and name of the ureteral stent used in the operative report. This data will be collected through the ROCKS clinical registry.

Section 8.3: Post-Operative

The patient's post-operative care will proceed per standard of care, and their follow up, imaging and clinic visits will be directed by the local surgeon according to their local protocol. All patients will be provided with the MUSIC pain optimization pathway (POP) medication for post-operative symptoms for ureteroscopy. The standard within MUSIC is to prescribe non-steroidal anti-inflammatory drugs (NSAIDs), alpha-blockers and an anti-cholinergic as first line therapy. Opiate pain medication is not recommended as first line therapy. Patients will also be provided the MUSIC pain management and stent specific education brochures.

The BLUES study is pragmatic. Stents will be removed at a time and duration per the surgeon's discretion. The patient's information regarding post-operative course will be collected into the registry 60 days after the surgery, keeping with current practice for MUSIC ROCKS patient registry entry.

Specific assessments obtained on the postoperative day 1 through 10, include:

- ROCKS PRO day 7 questionnaire
  - Participants will complete their day 7 ROCKS PRO questionnaire, consisting of PROMIS® scores of pain intensity and interference, LURN SI-10 score Baseline ICIQ-S score, stent specific USSQ question and reported number of days off work (Figure 1)
- Ecological Momentary Assessment (EMA) measured via daily text message
  - Participants will complete a single visual analog scale survey for pain and one functional ability question from the PROMIS® ability to participate in social roles and activities (Figure 2)

Specific assessments obtained on the postoperative day ≤ 60, include:

- ROCKS PRO 4-week questionnaire

    - Participants will complete their 4-week postoperative ROCKS PRO questionnaire, consisting of PROMIS® scores of pain intensity and interference, LURN SI-10 score Baseline ICIQ-S score, stent specific USSQ question (Figure 1)
- Stone-free rates within 60 days
    - Participants after URS are often requested to obtain renal imaging within 8 weeks. However, since this is a pragmatic study, patients are asked to receive imaging based on provider discretion, and some patients do not attend their imaging appointment, Utilizing MUSIC and ROCKS existing infrastructure. Stone free defined as no residual fragments identified on any postoperative imaging (ultrasound, abdominal X-ray, CT or any combination) within 60 days

Section 8.4: Concomitant Medications/Treatments
During this study, participants are asked to adhere to the recommendations of their treating surgeon. The use of the MUSIC ROCKS physician pain medication guidance and patient specific educational resources for ureteroscopy and stenting is recommended.

Section 8.5: Other Modalities or Procedures
Not applicable.

Section 8.6: Duration of Therapy
At the end of ureteroscopic procedure, a ureteral stent will be placed by the urologist in the standard fashion that each urologist is trained to perform. Stent sizing, technique, duration and removal technique will be determined by the individual urologist and their standard practice.

Patient study period will not exceed 60 days postoperatively unless related to a serious adverse event (SAE).

Section 8.7: Off Treatment Criteria
A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the SoA, and is >60 days after their procedure.

Section 8.8: Duration of Follow-Up
60 days postoperatively unless related to a serious adverse event (SAE).

Section 8.9: Off Study Criteria
Discontinuation from the BLUES study does not mean discontinuation from the study. No temporary discontinuations will be allowed due to short term patient participation. The pragmatic nature of the study enables continued standard of care postoperative care as directed by their treating urologist. Patients will have been enrolled into MUSIC ROCKS and ROCKS PRO. Study procedures as indicated by the study protocol will be tracked and recorded. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported if necessary as defined in section 10.

The data to be collected at the time of study intervention discontinuation will include the following:

- Participant, treating urologist and/or local PI will contact the local study team member or the BLUES study team directly with the following:
    - Specific underlying reason for discontinuation

The local site study team member will notify the BLUES study team to ensure the participant discontinuation status is recorded if the BLUES study team was not contacted directly.

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Significant study SoA non-compliance
    - No phone call, text message or email responses per SOA or study coordinator inquiries
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to receive phone calls, text messages or email for 5 of the 10 days postoperatively.

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF) by the local study team member. Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

Section 8.10: Patient Replacement
Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

Subjects who are found to be ineligible at any time prior to ureteral stent placement may be replaced.

Section 9: STUDY PROCEDURES
Time and Events Table

Procedures	Baseline Evaluation	Prior to operation	Operative Day	Ambulatory Assessments Days 1-10	Ambulatory Assessment Day 7 [2]	Postoperative visit: Stent removal	Ambulatory Assessment Week 4 [3]	Day ≤ 30	Day ≤ 60
Informed consent		X							
Study education		X							
Demographics	X								
Medical history	X								
Randomization			X						
Study intervention				X					
Radiologic imaging assessment [1]	X								
Daily EMA				X					
ROCKS PRO		X			X		X		
Follow-up assessments of study endpoints and safety								X	X
Complete Case Report Form (CRF)			X			X		X	X

[1]: Urological imaging modality performed nearest to but prior to operative date.
[2]: Day 7 ambulatory assessment can be completed from post-operative day 7 through day 10.
[3]: Week 4 ambulatory assessment can be completed from post-operative day 22 through day 42.

Section 10: ADVERSE EVENTS

Section 10.1: Adverse Event Reporting Requirements
Adverse event (AE) monitoring and reporting is a routine part of every clinical trial and is done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Data on adverse events will be collected from the time of the initial study intervention through 30 days after the study intervention. Any serious adverse event that occurs more than 30 days, and before 60 days of the study intervention and is considered related to the study intervention must also be reported. Serious Adverse Events (SAEs) will continue to be followed until:

- Resolution or the symptoms or signs that constitute the serious adverse event return to baseline;
- There is a satisfactory explanation other than the study intervention for the changes observed; or
- Death.

The investigator is responsible for the detection, documentation, grading, and assignment of attribution and expectedness of events meeting the criteria and definition of an AE or SAE. The definitions of AEs and SAEs are given below. It is the responsibility of the principal investigator to ensure that all staff involved in the trial is familiar with the content of this section.

Any medical condition or laboratory abnormality with an onset date before the initial study intervention will be considered pre-existing in nature. Any known pre-existing conditions that are ongoing at the time of study entry should be considered medical history.

For this study, non-serious AEs will not be reported to the IRB. SAEs will be reported in keeping with the governing IRBs guidelines.

Section 10.2: Definitions

1. Adverse Event
For the purposes of this trial, an adverse event (AE) is considered any untoward medical occurrence in a patient receiving study treatment that has or potentially has a causal relationship with this treatment. Any untoward medical occurrences that are unrelated to the study intervention will not be considered adverse events.

Symptoms of kidney stone disease and expected side effects from ureteroscopy lithotripsy and stent placement are not considered adverse events for this study. The following symptoms are indicative of underlying kidney stone disease and expected side effects from ureteroscopy with laser lithotripsy and stent placement, and will not be reported as adverse events (unless the event meets the criteria of an SAE):

- Hematuria
- Irritative voiding symptoms (e.g., urinary frequency, urgency, dysuria)
- Abdominal/flank/bladder pain
- Nausea and/or vomiting
- Dizziness and lightheadedness
- Urinary retention

Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms or require therapy. They are to be captured under the signs, symptoms, or diagnoses associated with them.

2. Serious Adverse Event
An adverse event is considered “serious” if, in the view of the investigator, it results in any of the following outcomes:

- Death
    - If death results from (progression of) the disease, the disease should be reported as an event (SAE) itself.
- A life-threatening adverse event

  - An adverse event is considered 'life-threatening' if, in the view of either the investigator [or sponsor], its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization for > 24 hours.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important medical event
  - Any event that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition of "Serious Adverse Event". Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that do not result in inpatient hospitalization or the development of drug dependency or drug abuse.

Hospital visits for conditions not associated with the urinary stone will not be collected or reported as SAEs.

3. Expected Adverse Event
An adverse event (AE) is considered "expected" if it meets the criteria of an AE per section 10.2, and is a known risk of general anesthesia and ureteroscopy such as:

- Myocardial infarction, deep vein thrombosis, cerebrovascular accident, pulmonary embolism, fever, UTI, sepsis, perinephric hematoma, acute kidney injury, ureteral injury or perforation, ureteral stricture or scarring, stent migration or dislodgement, stent encrustation

4. Unexpected Adverse Event
An adverse event (AE) is considered "unexpected" if it meets the criteria of an AE per section 10.2, and is not expected as described above.

Section 10.3: Reporting of Unanticipated Problems
Upon becoming aware of any incident, experience, or outcome (not related to an adverse event) that may represent an unanticipated problem, the investigator should assess whether the incident, experience, or outcome represents an unanticipated problem. The incident, experience or outcomes is considered unanticipated if it meets all of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency);
2. Related or possibly related to participation in the research; and
3. Suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.

If the investigator determines that the incident, experience, or outcome represents an unanticipated problem, the investigator must report it to the IRB according to the local IRB policies.

Section 10.4: Unblinding Procedures
To minimize bias in patient-reported outcome measures, all reasonable efforts will be made to keep patients blinded to their randomized treatment allocation. This will help to assure that all patient-reported outcomes and clinical data collection for the trial have been completed prior to unblinding. Patients will be notified of their randomized treatment allocation by trial staff at the coordinating center at the conclusion of the study.

In the case of a medical emergency or other event in which the participant's knowledge of their treatment allocation is critical to the participant's clinical management, the blinding for that participant may be broken by the investigator. The investigator or their designee must document the date and reasons for such emergency unblinding in the participant's source documents. The investigator must also immediately notify the study PI and trial coordinating center of such an event.

Section 10.5: Stopping Rules
An interim analysis for futility is planned after accrual of 112 patients. The study will stop early if it is found that the silicone stent arm has clinically significant worse pain intensity and worse pain interference at 7 days with worse pain defined as 5 or greater t-score points worse pain in the silicone stent arm compared to the non-silicone stent arm after adjusting for baseline. Under the alternative hypothesis for both endpoints simulations of 1000 trials estimates the probability of stopping early is 0%. If we assume that the silicone stent is worse than the non-silicone stent by 5 points simulation of 1000 trials estimates the probability of stopping early is 24.4%.

Section 11: STATISTICAL CONSIDERATIONS
Section 11.1: Statistical Hypotheses
This is a multi-center two-arm stratified, randomized comparative effectiveness study in patients are treated with URS for nephrolithiasis with a planned placement of a stent to assess patient reported quality of life. The primary hypothesis is that the silicone ureteral stent arm will have superior patient reported pain outcomes compared to the non-silicone stent arm. Patients will be stratified by stone location (kidney only / ureteral) and randomized to receive a silicone stent or a non-silicone stent and complete the PROMIS® pain intensity and PROMIS® pain interference surveys prior to surgery and at 7 days after stent placement.

Our formal statistical hypotheses are:

H_0: $\mu_{ns} = \mu_{ss}$, H1: $\mu_{ns} \neq \mu_{ss}$
where, μ_{ns} = mean PROMIS® pain intensity in non-silicone stent arm at 7 days
μ_{ss} = mean PROMIS® pain intensity in silicone stent arm at 7 days

AND

H_0: $w_{ns} = w_{ss}$ H1: $w_{ns} \neq w_{ss}$
where, w_{ns} = mean PROMIS® pain interference in non-silicone stent arm at 7 days
w_{ss} = mean PROMIS® pain interference in silicone stent arm at 7 days

Section 11.2: Power/Sample Size:
Assume that the correlation of baseline is 0 for purposes of the sample size calculation. If this assumption is violated, the power for each hypothesis will be greater than the stated power.

A clinically meaningful change in pain PROMIS® score is between 4 and 6 and the standard deviation of the score is 10(16-18). Assuming a 5 t-score PROMIS® pain point difference between 2 arms and a standard deviation of 10, a t-test including 101 patients per arm has 90% power with a 2-sided alpha = 0.025. Assuming a 10% loss-to-follow-up, accrual of 224 study treated patients (112 patients per arm) is planned. Our planned analysis does not match this calculation because we will adjust for the baseline pain to ensure any imbalance prior to surgery is accounted for. However, this power calculation, by ignoring the adjustment of baseline pain, is accurate if the correlation of baseline pain with our outcome is 0. If the correlation is greater than 0, then we will have more power than described.(19)

Section 11.3: Populations for Analyses
Modified Intent-to-Treat (m-ITT) Population: All participants eligible and randomized who complete the pain intensity and pain interference questionnaire between 7-10 days post-URS will be included. Subjects will be analyzed by assigned treatment at randomization. This is the main population for efficacy analyses.

Per-Protocol Population: All Patients eligible and randomized patients who complete the pain intensity and pain interference questionnaire between at 7 days post-URS will be included per treatment arm received. This second population will be used to assess the robustness of the primary and secondary efficacy outcomes.

Safety Population: All patients who are randomized and receive a stent will be define the safety population and used for all safety analyses. Subjects will be analyzed by assigned treatment arm.

Section 11.4: Statistical Analyses

General Approach

Descriptive statistics for the study population will be reported using frequentist statistics. In general, continuous measures will be reported using means and standard deviations or medians and the interquartile range as the distribution warrants. Categorical variables will be reported as counts and proportions.

Analysis of the Primary Efficacy Endpoints

The primary endpoints of the study are PROMIS® pain intensity and PROMIS® pain interference t-scores. Each endpoint will be analyzed separately using an ANCOVA model for each. Using the mITT population for analysis, the t-score of the PROMIS® outcome at 7 days post-URS will be the dependent variable and treatment arm and pre-treatment (baseline) PROMIS t-score will be independent variables. The primary comparison of interest is treatment arm. The baseline adjusted mean pain score at 7-days will be reported by arm with the 97.5% confidence interval and a type-3 F-test will test the hypothesis that pain differs between the two treatment groups. Each endpoint modeled will test the effect of treatment arm adjusting for baseline with a type I error of 2.5% for an overall study type I error of 5%.

An analysis in the per-protocol population will be assess the robustness of the effect found in the primary analysis. Additionally, a multivariable model will be considered to account for other patient or surgical variables that may be unbalanced between the arms including timing of stent removal or stone location.

Analysis of the Secondary Endpoints

Additional health-related quality of life endpoints including PROMIS® Pain scores at 4 weeks will be analyzed with similar models described for the primary endpoint. A linear mixed model will be used to compare LURN SI-10 scores at 7 days and 4 weeks between treatment arms. Each analysis will report means with 95% confidence intervals at each time for each arm with a model based type-3 F-test comparing treatment arms.

Healthcare utilization within 30 days of URS will be assessed using a composite endpoint. The composite healthcare utilization metric within 30 days will be a composed score based upon utilization by the patient with each patient assigned a score based upon the highest utilization level that they participate in with levels defined in decreasing order:

5. Hospitalization and ICU care
4. Unplanned hospitalization
3. Emergency department visit
2. Ambulatory encounter: Clinic visit
1. Ambulatory encounter: Phone call or message

We will compare the composite score ranking between the treatment arms using a WinRatio analysis using the unmatched approach.(20) The median composite score for each arm will be reported, along with the WinRatio and associated 95% confidence interval and p-value.

Abnormal imaging and stone-free rates will each be summarized as a count with the associated proportion by treatment arm and tested with a chi-square test (or fisher’s exact test if event counts are 5 or less.)

Planned Interim Analyses

An interim analysis for futility is planned after accrual of 112 patients. The study will stop early if it is found that the silicon stent arm has clinically significant worse pain intensity and worse pain interference at 7 days with worse pain defined as 5 or greater t-score points worse pain in the silicone stent arm compared to the non-silicone stent arm after adjusting for baseline. Under the alternative hypothesis for both endpoints simulations of 1000 trials estimatas the probability of stopping early is 0%. If we assume that

the silicone stent is worse than the non-silicone stent by 5 points simulation of 1000 trials estimates the probability of stopping early is 24.4%.

Sub-Group Analyses
A sub-group analysis by stone location is planned. Primary and secondary endpoints will be reported for ureteral stones separately from renal stones.

Exploratory Analyses.
The mean (with standard deviation) or median (with interquartile range) days taken off work by patient and separately by caregiver will compared between treatment arms with a t-test or Wilcoxon rank test if the distribution warrants.

Ecological Momentary Assessments of pain and PROMIS® daily ability to participate in social roles and activities score measured via daily text message will displayed using spaghetti plots. Each measure will be analyzed with a linear mixed model including fixed effects of treatment arm, day, and the interaction of treatment arm and day. As this is an exploratory endpoint, these models will be explored using several methods to address missing data and model fit.

Each healthcare utilization metric within 30 days of URS will be summarized separately as a count with the associated proportion by treatment arm and tested with a chi-square test (or fisher's exact test if event counts are 5 or less.)

In an exploratory analysis to create a composite endpoint to be used in future trials we will assess the plausibility of 2 composite measurement plans and analyses of these.
In addition to the WinRatio, our second composite analysis will include healthcare utilization and PROMIS® Pain. Additionally, we will use a composite score ranking of healthcare utilization similar to the WinRatio plan and add the PROMIS® Pain scores to the analysis using DOOR. The probability that a randomly selected patient will have a better DOOR if assigned to the silicone stent will estimated.(21) The WinRatio and DOOR composite healthcare utilization metric ratios' sizes and directions will be compared.

The number and proportion of patients who are prescribed opioid medications will be reported by arm and compared using a chi-square test.

Satisfaction score assessed using the ICIQ-S will be summarized at 7 days and 4 weeks by arm with means and standard deviations. A repeated measures model will be used to test if satisfaction differed at either time between treatment arms using an interaction of time and arm.

Section 12: DATA AND SAFETY MONITORING
The DSMC will consist of the MUSIC ROCKS Program Manager, Program Director, Statistician, and other members of the MUSIC ROCKS team. This committee is responsible for monitoring the safety and data integrity of the study.

Each performance site's local study team is required to meet virtually with the DSMC and BLUES study team every six months if it is determined by the DSMC and/or Principal Investigator that a virtual meeting is necessary. The discussion may include matters related to the safety of study participants (Serious Adverse Event, Adverse Event and Unanticipated Problem reporting), completeness, validity and integrity of the study data, enrollment rate relative to expectations, characteristics of participants, retention of study participants, and adherence to the protocol (potential or real protocol deviations). If there are no concerns around any of the aforementioned items, the principal investigator and/or the DSMC may decide that a meeting is unnecessary and if so, a progress summary communication will serve in it's place. Additionally, a member of the BLUES study team will send a communication summarizing current progress to each site on a monthly basis. These communications will consist of 1) any identified Serious Adverse Events and necessary follow-up, 2) enrollment rate relative to expectations, and 3) any identified protocol deviations, unanticipated problems, and recommendations to prevent additional instances.

These 6-month meetings are to be documented by the BLUES study coordinator or the BLUES trial project manager and will include the topics listed above as appropriate. The meeting minutes must be signed by the Principal Investigator or by one of the co-investigators.

The BLUES study team is responsible for collating all the meeting documentation for participating sites and will report any serious adverse events, unanticipated problems, and protocol deviations as outlined in section 10.

Section 13: QUALITY ASSURANCE AND AUDITS

The Data and Safety Monitoring Committee can request a 'for cause' quality assurance audit of the study if the committee identifies a need for a more rigorous evaluation of study-related issues.

A regulatory authority (e.g. FDA) may also wish to conduct an inspection of the study, during its conduct or even after its completion. If an inspection has been requested by a regulatory authority, the site investigator must immediately inform the BLUES study team that such a request has been made.

Section 14: CLINICAL MONITORING PROCEDURES

Prior to subject recruitment, a participating site will undergo site initiation meeting to be conducted by the BLUES study team. This will be done as a teleconference, videoconference, or web-based meeting after the site has been given access to the study database, provided the BLUES study team the necessary regulatory documentation and received IRB approval. The site's principal investigator and study staff should make every effort in attending the site initiation meeting. Study–related questions or issues identified during the site initiation meeting will be followed-up by the appropriate BLUES study team personnel until they have been answered and resolved.

Monitoring of this study will include centralized surveillance of study specific MUSIC registry data by the BLUES study team to confirm adherence to the protocol. The BLUES study team will meet at least once per month to review findings of surveillance and may engage sites ad-hoc as appropriate. Additional monitoring will be performed by the BLUES study staff members on an annual basis.

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FIGURES

Figure 1. ROCKS PRO Questionnaire

ROCKS PRO PROMIS® Pain Intensity and Interference

	Had no pain	Mild	Moderate	Severe	Very severe
1. How intense was your pain at its worst?	○	○	○	○	○
2. How intense was your average pain?	○	○	○	○	○
3. What is your pain right now?	○	○	○	○	○
	Not at all	**A little bit**	**Somewhat**	**Quite a bit**	**Very Much**
4. How much did pain interfere with your enjoyment of life?	○	○	○	○	○
5. How much did pain interfere with your ability to concentrate?	○	○	○	○	○
6. How much did pain interfere with your day to day activities?	○	○	○	○	○
7. How much did pain interfere with your enjoyment of recreational activities?	○	○	○	○	○
8. How much did pain interfere with your tasks away from home (e.g. getting groceries, running errands)?	○	○	○	○	○
	Never	**Rarely**	**Sometimes**	**Often**	**Always**
9. How often did pain keep you from socializing with others?	○	○	○	○	○

ROCKS PRO LURN-S10

Instruction: This questionnaire asks you about different urinary symptoms. Please read each question carefully, and then circle the response that best describes your symptoms.

	Never	A few times	About half the time	Most of the time	Every time
1. In the past 7 days, how often did you feel a sudden need to urinate?	0	1	2	3	4
2. In the past 7 days, how often did you leak urine or wet a pad after feeling a sudden need to urinate?	0	1	2	3	4
3. In the past 7 days, how often did you leak urine or wet a pad while laughing, sneezing, or coughing?	0	1	2	3	4
4. In the past 7 days, how often did you leak urine or wet a pad when doing physical activities, such as exercising or lifting a heavy object?	0	1	2	3	4
5. In the past 7 days, how often did you have pain or discomfort in your bladder while it was filling?	0	1	2	3	4
6. In the past 7 days, how often did you have a delay before you started to urinate?	0	1	2	3	4
7. In the past 7 days, how often was your urine flow slow or weak?	0	1	2	3	4
8. In the past 7 days, how often did you dribble urine just after zipping your pants or pulling up your underwear?	0	1	2	3	4
Circle number here --->	0	1	2	3	
9. In the past 7 days, during waking hours, how many times did you typically urinate?	(3 or fewer times a day)	(4-7 times a day)	(8-10 times a day)	(11 or more times a day)	
Circle number here --->	0	1	2	3	
10. In the past 7 days, during a typical night, how many times did you wake up and urinate?	(none)	(1 time)	(2-3 times)	(More than 3 times)	

ROCKS PRO ICIQ-S

Answer the following questions thinking about how satisfied you were with the treatment or surgery that you had. All the information you give us is confidential.

1. **How would you rate the outcome of your surgery?**

very successful	4
somewhat successful	3
neither successful nor unsuccessful	2
a little unsuccessful	1
very unsuccessful	0

2. **Compared to how you felt before your surgery, how is your condition now?**

much better	4
a bit better	3
about the same	2
a bit worse	1
much worse	0

3. **Would you say you have been able to return to a 'normal life' after your surgery?**

strongly agree (or I was not limited before)	3
agree	2
disagree	1
strongly disagree	0

4. **If you were in the same situation again, would you still have the surgery?**

yes, definitely	4
yes, probably	3
not sure	2
no, probably not	1
no, definitely not	0

5. **Would you recommend this surgery to friends or relatives with similar problems?**

yes, definitely	4
yes, probably	3
not sure	2
no, probably not	1
no, definitely not	0

6. **If you had to spend the rest of your life with your symptoms as they are now, how would you feel?**

perfectly happy (or I no longer have any symptoms)	5
somewhat happy	4
mixed feelings	3
somewhat unhappy	2
very unhappy	1
desperate	0

ROCKS PRO Time Off Work

Within the last week, did you miss any days of school or work?	◯ Yes ◯ No ◯ I do not currently work/I am not currently in school
If yes, please enter how many days of school or work were missed.	_____
Within the last week, has your parent/caregiver missed work?	◯ Yes ◯ No ◯ My parent/caregiver does not currently work
If yes, please enter how many days of work your parent/caregiver has missed.	_____

ROCKS PRO USSQ

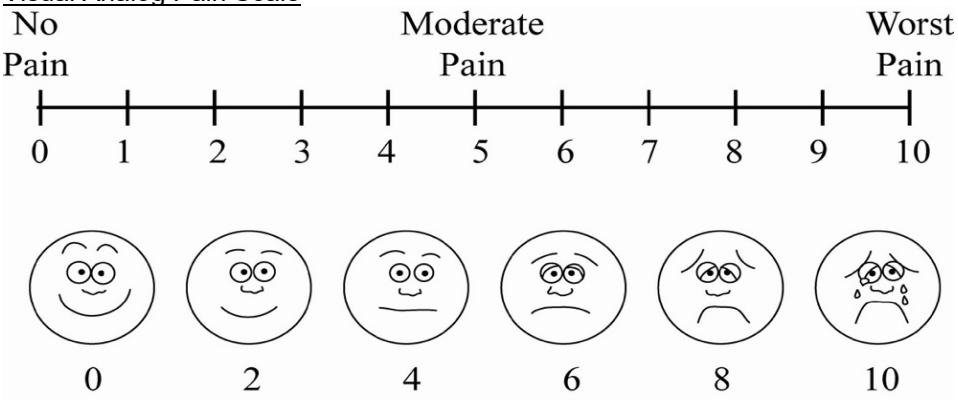
USSQ question concerning stent

Instruction: Answer the question below if you had a stent placed during the surgical procedure otherwise select N/A.

	Delighted	Pleased	Mostly Satisfied	Mixed Feelings	Mostly Dissatisfied	Unhappy	Terrible	Not Applicable (N/A)
In the future, if I were advised to have another stent inserted, how would I feel about it?								

Figure 2. Daily Ecological Momentary Assessment

Visual Analog Pain Scale



PROMIS® Ability to Participate in Social Roles and Activities – Short Form 4a Questionnaire

		Never	Rarely	Sometimes	Usually	Always
SRPPER23_ CaPS	I have trouble doing all of my usual work (include work at home)	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Figure 3. BLUES Patient Reported Outcomes: Flow Chart

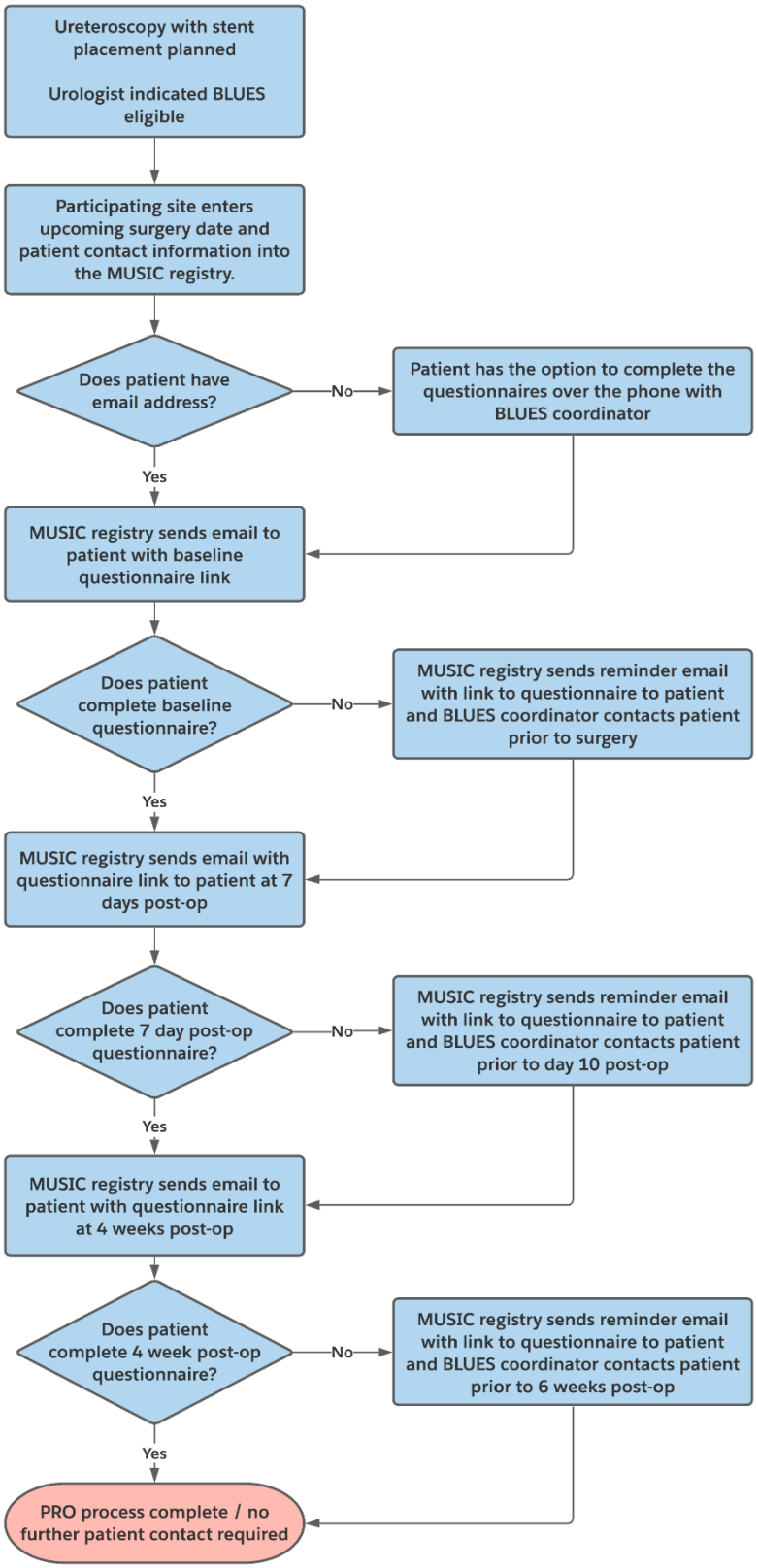
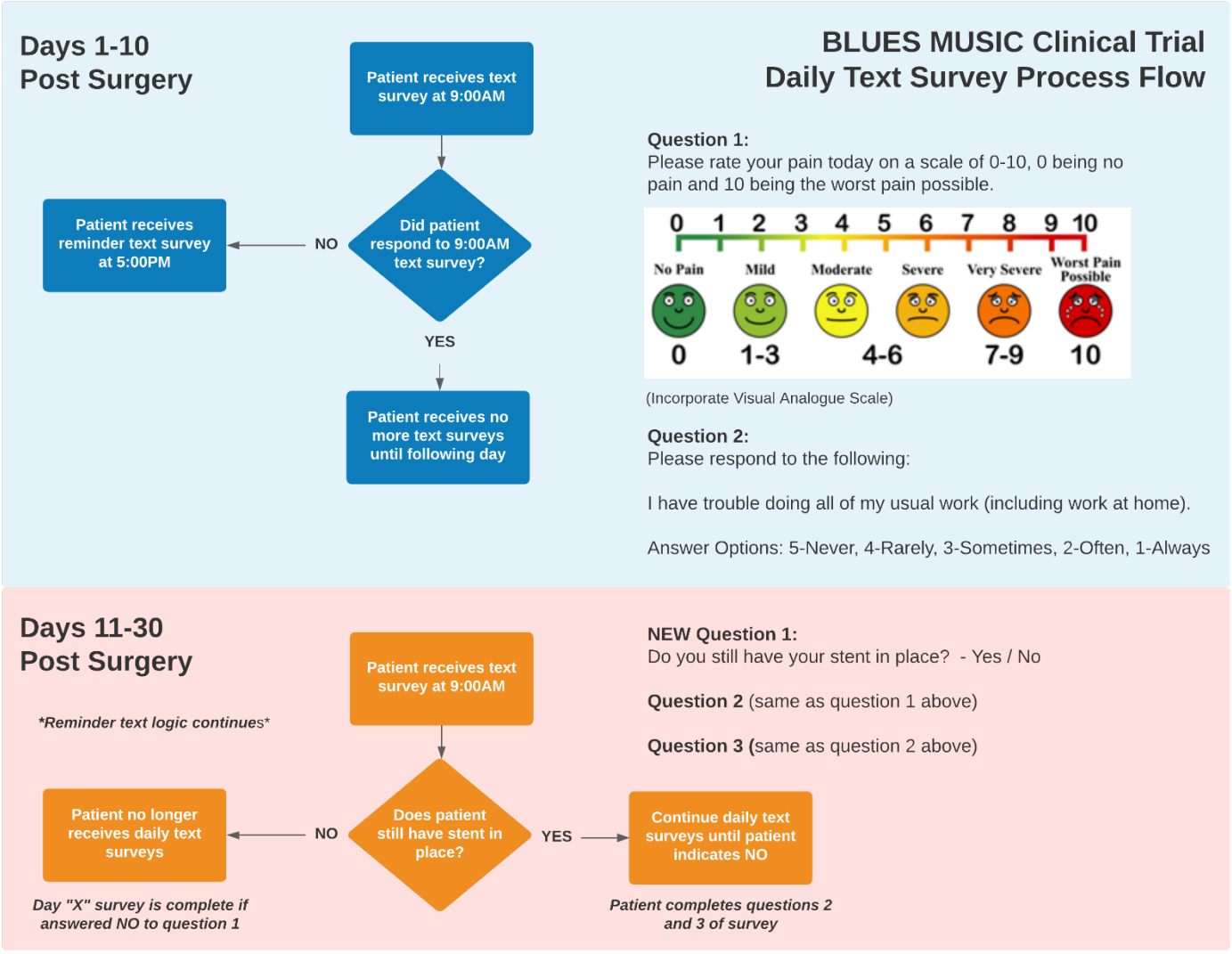


Figure 4. BLUES Ecological Momentary Assessments (EMA) – Daily Text Survey: Flow Chart



APPENDICES

Appendix 1. Heat map of appropriateness for ureteral stent omission after URS according to panelists

			Pre Stented					
			Negative Culture					
			Size ≤5mm		Size >5mm - ≤10mm		Size >10mm - ≤15mm	
			Ureter	Kidney	Ureter	Kidney	Ureter	Kidney
No Dilation	UAS -	Frag -	9	9	9	9	7	7
	UAS +	Frag -	8	8	8	7	6	6
	UAS -	Frag +	7	7	7	6	5	4
	UAS +	Frag +	7	7	6	5	3	4

			Not Pre Stented					
			Negative Culture					
			Size ≤5mm		Size >5mm - ≤10mm		Size >10mm - ≤15mm	
			Ureter	Kidney	Ureter	Kidney	Ureter	Kidney
No Dilation	UAS -	Frag -	9	9	7	7	5	4
	UAS +	Frag -	3	3	3	2	2	2
	UAS -	Frag +	6	5	3	2	2	1
	UAS +	Frag +	3	2	2	2	1	1
Dilation	UAS -	Frag -	4	4	3	3	2	1
	UAS +	Frag -	3	2	2	2	1	1
	UAS -	Frag +	3	2	2	2	1	1
	UAS +	Frag +	2	1	1	1	1	1

Highly Appropriate	Appropriate	Uncertain	Inappropriate	Highly Inappropriate
Median = 9	Median = 7-8	Median = 4-6	Median = 2-3	Median = 1

UAS +, ureteral access sheath used. UAS -, no ureteral access sheath used. Frag +, basketable residual fragments left. Frag -, no basketable residual fragments left