The RELIEF™ Ureteral Stent – Assessment of Retrograde Urinary Reflux and Distal Coil Bladder Position

NCT03266770

11/29/2021

Objectives

Primary Objectives:

- Evaluation of the stent placement and the adequacy of short term drainage (defined as the presence of the stent in the ureter and the lack of surgical or other intervention to treat symptoms associated with the stent itself on the stented side during the first 48 hours).

Secondary Objectives:

- Assessment of retrograde urine reflux after placement of the RELIEF® Ureteral Stent using cystography after contrast gravity-filling of the bladder and assigning a urinary reflux grade based on:
    - Grade I: urine refluxes into the ureter only.
    - Grade II: urine refluxes into the ureter and up to the kidney without dilation.
    - Grade III: urine refluxes into the ureter and kidney and causes mild dilation.
    - Grade IV: urine refluxes into ureter and kidney and causes dilation without twisting of the ureter.
    - Grade V: urine refluxes into ureter and kidney and causes significant dilation with twisting of the ureter.
- Visualization of distal coil in bladder, after RELIEF Stent placement. Document placement using a cystoscope and obtain image, if possible.
- Assessment of adverse events (incidence, relationship to device, severity) attributed to the Ureteral Stent, compared to established adverse event rates from published clinical studies and FDA reportable event occurrences, compared to number of US annual ureteral stent placements.
- Reporting the Ureteral Stent Symptoms Questionnaire before stent placement, after placement and prior to removal.

Background

Traditional ureteral stents are commonly used in practice to relieve renal obstruction or as a scaffold to promote healing after endoscopic or open/ laparoscopic surgeries involving the ureter [1]. However, there are a lot of morbidities that can be associated with placing these stents either due to irritation of the bladder or affection the kidney.

The most commonly reported symptoms include urgency, urinary frequency, dysuria, incontinence, hematuria, suprapubic discomfort, fever due to urinary tract infections and flank pain and they can occur in up to 80% of stented patients. Sometimes, the symptoms are poorly tolerated and can negatively affect the patient quality of life [2, 3].

Shao et al have studied the relationship between bladder filling and the renal pelvic pressure (RPP) in stented patients, which revealed that RPP has increased mildly during bladder filling and dramatically during voiding indicating urinary reflux and encouraged on early removal of the stents [4]. Another study showed that patients with stents whose distal coils crossing the midline are at higher risk of poststenting morbidities [5].

From a theoretic point, replacing the distal part with a thin material can reduce the bladder irritative symptoms and allow the ureterovesical junction to coapt and thereby, eliminating urinary reflux [6]. The Ureteral Stent Company, LLC (USC) is developing the RELIEF™ Ureteral Stent, a single use, disposable ureteral stent (US) device that will provide the traditional function of allowing the passage of urine from the kidney to the bladder with two design enhancements to improve patient care:

- A low-profile tether through the intramural ureter segment, minimizing the potential of urinary reflux
- Polymeric solid distal coil that minimizes the potential for coil positioning on the trigone, reducing potential of associated bladder spasms and pain.

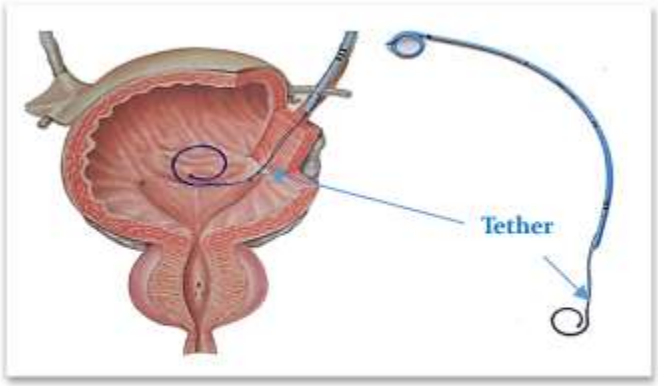


Figure 1. Illustration of RELIEF™ Stent *in situ* (left) and Stent Image (right)

As presented in the RELIEF™ Ureteral Stent Regulatory Plan, Matrix Report R-40-001.4, the RELIEF™ Ureteral Stent is intended to relieve proximal and middle third obstruction in a variety of benign, malignant and post-traumatic conditions in the ureter. These conditions include stones and/or stone fragments or other ureteral obstructions such as those associated with ureteral stricture, malignancy of abdominal organs, retroperitoneal fibrosis or ureteral trauma, or in association with Extracorporeal Shock Wave Lithotripsy (ESWL). The stent may be placed using endoscopic surgical techniques or percutaneously using standard radiographic technique. The stent is not intended as a permanent indwelling device.

We hypothesize that the RELIEF stent will offer the same function of the traditional stents with the added benefits of 1) prevention of urinary reflux and 2) reduction of irritative bladder symptoms.

Inclusion and Exclusion Criteria

	Inclusion Criteria
1.	*Male and female patients*
2.	*Over 18 years of age and willing and able to provide informed consent*
3.	*Renal or ureteral stone of 5-25 mm measured on plain abdomen X-ray KUB (Kidney Ureter Bladder) or CT (computed tomography)*
4.	*Upper or middle third ureteral stricture or stone AND/OR stone located in the renal pelvis*
5.	*Patient agrees to participate in the study and signs the informed consent form*
6.	*Able to complete self-rated questionnaires*

	Exclusion Criteria
1.	*Patients with distal ureteral obstruction*
2.	*Patients with urinary reflux (assessed by pre-stent cystogram)*
3.	*Patients requiring bilateral surgical stone management procedure or patients with active urinary tract infection (UTI) or sepsis*
4.	*Intraoperative exclusion: Based on the urologist's discretion, if trauma has been induced to the distal ureter due to ureteroscopy maneuvers, exclude these patients.*

Number of Research Participants

We plan to enroll a minimum of 20 patients, not to exceed 30 patients at UHCMC.

Recruitment Methods

Following Institutional Review Board (IRB) approval of the proposed study, patients will be identified during their clinic visits to one of the Endourology providers at UH and will undergo a standard consultation to discuss all available treatment options. Patients who are deemed clinically suitable to undergo the RELIEF Stent and choose to participate will be screened utilizing the EMR for recruitment. The urology provider will first determine if they are interested in participating in the research study and upon agreement, a study team member or research coordinator will introduce the study details and initiate a consent interview. If eligible, these patients will be approached during pre-surgical preoperative clinic or inpatient visits by the research team to further explain the study and further address any of their questions and get their consent. Patients will be free to leave the study without any impact or influence on their clinical care or management at any point should they desire to do so.

Setting:

1) UH Cleveland Medical Center, UH Richmond Medical Center, UH Ahuja Medical Center, UH St. John Medical Center, UH Brainard Medical Building (29001 Cedar Rd, Suite 202, Lyndhurst OH, 44124), and UH Beachwood Medical Center
2) Patients will be identified during their clinic visits to one of the UH Endourology providers
3) UH main campus Lakeside: 4559 and UH Beachwood Medical Center

Consent Process

Eligible subjects will be consented by a Research Nurse or Investigator prior to the procedure.

Study subjects will be asked to sign the Informed Consent at the time of admission for procedure.

All subjects should be familiar with the Informed Consent and its content, and have been given opportunity to have their questions answered about the study prior to signing the Informed Consent. At the time of admission, the patient will be assessed for suitability. If the patient meets the inclusion/exclusion criteria, he/she will enter the study.

Results will be shared with ONLY the research participants' doctors who are among the approved study team by the UH IRB.

Study Design

Allocation: Non-randomized

Endpoint Classification: Safety/Efficacy Study

Intervention Model: Single Group Assignment

Masking: Open Label

Primary Purpose: Treatment

Study Procedures

Informed Consent: Eligible subjects will be consented by a Research Nurse or Investigator prior to the procedure.

Inclusion Criteria: Confirmation of fulfilling Inclusion criteria (e.g., consent, examination, indication) and that subject does not have any Exclusion criteria.

Pre-Stenting Evaluation (Day 0 or within 24 hours of Day 0): USSQSurvey and 10 -Point Pain Score: Subject completesUSSQsurvey for baseline evaluation (pre-stenting, Day 0)

Ureteral Stenting Procedure (Day 0):

Pre-stent cystogram

• Instill dye (up to 300 cc) under gravity-filling cystogram for assessment of pre-stent reflux and capture Xray image (with C-arm). (Exclude patients with reflux). Cystogram image will be saved.

• Drain bladder

[CRF: Pre-Stent Reflux Result; Pre-Stent Cystogram Image]

Ureteral Stent Placement

• Obtain retrograde pyelogram.

• Insert guidewire and perform ureteroscopy for treatment when needed. (Based on the urologist's discretion, if trauma has been induced to the distal ureter due to ureteroscopy maneuvers, these patients will be excluded).

• Any remaining contrastshould be flushed by irrigation ofsaline. Confirmatory X-ray image may be captured to ensure that contrast has been adequately removed (Note: If residual contrast considered not acceptable or confirmatory X-ray not recommended,subject may be excluded from study and traditional stent used).

• Remove the pull-outsuture, then place RELIEF stent under cystoscopy. Stent with pusher placed over guidewire and inserted. Position pusher until reach 4 cm mark. Remove wire. Back-out pusher. Confirm xray image ofstent position and save the image.

[Case Report Form (CRF): Acceptable cystoscopy visualization or unusual/unforeseen observation(s) noted. Acceptable result of retrograde pyelogram. Observations noted, if any. Cystoscopy image and X-ray image saved. Confirmatory X-ray shows no/low residual contrast, considered acceptable for Study.]

Post-stent cystogram

• Instill dye (up to 300 cc) under gravity-filling cystogram for assessment of post-stent reflux.

• Drain bladder.

• Fill bladder with 150 cc saline up to 300 cc to assess whether distal coil ofstent istouching trigone (documented as “on” or “off”) at both volumes.

• Treat patient understandard of care.

CFR: DAY 0 – Stent Placement. X-Ray image; post-stent placement. Record post-stenting cystoscopy image, if possible. Record distal coil location. [CRF: Post-Stent Reflux Result; Post-Stent Cystogram Image]. Record Clinician Usability Survey results(from stenting placement procedure). [Considered: Day 0]

Post-stent Follow-Up:

• Post-operatively complete USSQ surveys at 24-48 hours post-stent placement, and at day 7-30 prior to removal of RELIEF stent.

• Day 1 (24-48 hours afterstenting procedure),subject will be evaluated by Clinician for acceptable procedural outcome.

• Subject will complete USSQ and 10-point pain scale surveys. [CRF: Successfully completed post-stent placement USSQ survey (attach) and record 10-Point Pain Score. Clinician examination resultsrecorded as acceptable, no further intervention warranted.]

• Day ofstent removal: Prior to stent removal procedure on day 7-30,subject will be asked to complete stent in situ USSQ and 10-point pain scale surveys. Subject will then be examined by Clinician with cystoscope and standard X-ray, if warranted. Ureteral orifice (with stent) will be evaluated for potential signs of irritation or inflammation with photograph taken if possible, a scale of 0-1-2 (Normal, mild inflammation, and moderate inflammation) will be used to grade orifice appearance. Stent removal will be performed by a standard of care approach (in-office cystoscopic removal). Stent will be evaluated for signs of encrustation and/or visually observable damage / dislocation or wear. Photograph stent. Clinician survey will be completed to assess usability for removal. Economic metric of removal time may also be included, if possible.

• If possible,subject will complete USSQ and 10-point pain scale surveys 1-2 days afterstent removal. If unusual level of pain or other potentially serious complicationssuspected,subject will be asked to come in for office visit and Clinician evaluation. [CRF: Record direct or remote subject evaluation and any unusual/ unexpected observation(s). Obtain successfully completed in situ USSQ survey (attach to CFR) and record 10-Point Pain Score. Record if subject directed to come in for clinician evaluation. Record post-stent evaluation and photograph, if possible. Record Clinician Usability Survey forstent removal. If possible,subject will complete post-stent removal USSQ survey (attach to CFR) and 10-Point Pain Score.] Afterseveral cases of the Relief Stent, an optionalsupplemental questionnaire may be completed by the provider regarding the use of the research device.

Study Timeline

Assessment	Screening and Stent Placement (Day 0)	Post-Stent Placement (24-48 hrs)	Day of Stent Removal (Stent *in situ*, Day 7-30)	Post-Stent Removal
Informed Consent Form	X			
General Physical Examination	X	X [In-office or remote evaluation]	X [In-office]	
Current Medications	X	X [In-office or remote evaluation]	X [In-office]	
Vital Signs	X	X [In-office or remote evaluation]	X [In-office]	
Indicated for Ureteral Stenting	X			
Inclusion/Exclusion Criteria	X			
Enrollment	X			
Ureteral Stent Symptoms Questionnaire	X	X	X [Before removal]	X [In-person or remote evaluation]
RELIEF® Ureteral Stent	X [Placement]		X [Removal]	
Additional Therapies, if needed	X	X	X	
Adverse Events	X	X	X	
Clinician Usability Survey	X [Placement]		X [Removal]	

Data to be Collected

- Patient demographics (Age, Sex, Race, BMI)

- Present and past history.

- Prior surgical procedures.

- Laboratory tests results,

- Any imaging results on the abdomen and pelvis.

- USSQ survey.

B. Intra-operative

- Total operative time
- Total fluoroscopy time
- Case Report forms as described before.

C. Post-operative

- USSQ survey.
- Case Report forms.
- Any complications/ adverse events.

Data Analysis Plan

Current enrollment number is designed to collect sufficient patient data to power a future, statisticallypowered clinical study to obtain an expanded FDA intended use claim for reduction in reflux and minimizes the potential for coil positioning on the trigone.

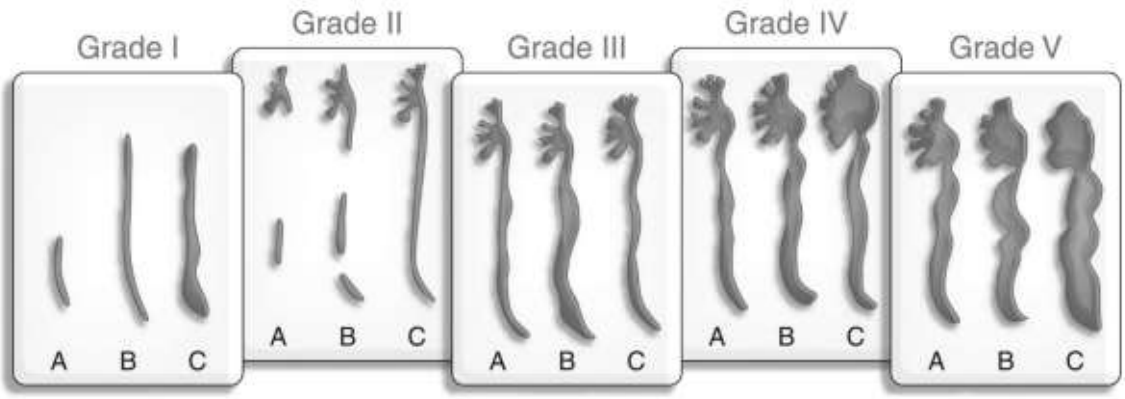
Study Endpoints:

1- **Primary effectiveness endpoint:**

• Study success defined as adequate short term drainage defined as the presence of the stent in the ureter and the lack of surgical or other intervention to treat symptoms associated with the stent itself or failure of the stent on the stented side during the first 48 hours [Day 0-2] following placement. [Note: In some cases, the ureteral stent may not be sufficient to relieve pain (not associated with stent specifically) and alternative surgical treatment may be warranted. In these cases, patient data will be captured but non-device related cause captured as reason for subject stenting termination.]

• Assessment of retrograde urine reflux after placement of the RELIEF® Ureteral Stent, as determined by the visualization of urine in the distal ureter to the kidney using cystography after contrast gravity-filling of the bladder and assigning a urinary reflux grade based on:

- Grade I: urine refluxes into the ureter only.
- Grade II: urine refluxes into the ureter and up to the kidney without dilation.
- Grade III: urine refluxes into the ureter and kidney and causes mild dilation.
- Grade IV: urine refluxes into ureter and kidney and causes dilation without twisting of the ureter.
- Grade V: urine refluxes into ureter and kidney and causes significant dilation with twisting of the ureter.



• Visualization of distal coil in bladder, after RELIEF Stent placement. Document placement using a cystoscope.

2- Primary safety endpoint:

• Assessment of adverse events (incidence, relationship to device, severity) attributed to the Ureteral Stent, compared to established adverse event rates from published clinical studies and FDA reportable event occurrences, compared to number of US annual ureteral stent placements. (No anticipated adverse events from Stent design; known complications from stenting may be observed.)

3- Secondary endpoint:

• USSQ Scale (Ureteral Stent Symptoms Questionnaire) [Time Frame: Day 0 (pre-stenting), 24-48 hours post-stent placement, and Day 7-30 prior to stent removal].

Stopping Rules: In the occurrence of any unexpected adverse events to the participants, the study team will hold study recruitment until the investigation is completed. Patients who experience unanticipated adverse events will have the RELIEF stent promptly removed.

Expected Adverse Events include:

• Flank pain/loin discomfort

● Flank pain when voiding

• Suprapubic pain/lower abdominal pain

● Trigonal irritation

• Urinary frequency

● Nocturia

• Urinary urgency

● Dysuria

• Urethral discomfort

● Incontinence

• Hematuria

● Stent migration

• Stent encrustation

● UTI

• Bacteriuria

● Signs of ureter trauma

• Additional stent specific procedures

Risks to Research Participants

There is a potential risk of loss of confidentiality of your data. Every effort will be made to keep the patients' information confidential.

The study participants may feel uncomfortable while addressing some of the questions in the pain questionnaire. They may refuse to answer any of these questions. They may stop their participation in this study at any time.

Ureteral stents are as a SoC procedure that is reported in the literature to be associated with adverse events including: • Flank pain/loin discomfort ● Flank pain when voiding • Suprapubic pain/lower abdominal pain ● Trigonal irritation • Urinary frequency ● Nocturia • Urinary urgency ● Dysuria • Urethral discomfort ● Incontinence • Hematuria ● Stent migration • Stent encrustation ● UTI • Bacteriuria ● Signs of ureter trauma • Additional stent specific procedures

In case any patient experiences any unexpected adverse events, the study team will hold study recruitment until the investigation is completed. Patients who experience unanticipated adverse events will have the RELIEF stent promptly removed.

Provisions to Protect the Privacy Interests of Research Participants

The study subjects will be reviewed in a private room or space and will be protected against viewing by any person either not on the study team or not currently caring directly for the subject. There will be no discussion outside closed doors regarding any information pertaining to data collected.

Potential Benefit to Research Participants

We assume that the potential benefits from participating in this study may include little to no backflow of urine to the kidney, less flank pain and less bladder irritative symptoms than the current standard of care. However, given that the stent is under investigation, these benefits cannot be guaranteed.

Withdrawal of Research Participants

Study participants will remain in the trial unless they choose to withdraw or they no longer meet the inclusion or exclusion criteria. Participants will be free to withdraw at any part of the study period without any influence on their treatment pathway or care.

Alternatives to Participation

If a patient chooses not to participate in this study, standard of care treatment will be provided.

Costs to Research Participants

The study will pay for all procedures/devices that are directly associated with this research study. This includes the RELIEF stent, and the extra x-rays. Procedures or drugs that are considered standard of care will be the responsibility of the patient or his/her insurance company

Research Participant Compensation

No compensation will be provided to study participants.

Provisions to Monitor the Data to Ensure the Safety of Research Participants

The group of investigators, including the principal investigator, and the research support staff (nurses, CMA's, data managers, and regulatory) will carry out the Data and Safety Monitoring Plan. Data will be reviewed quarterly to ensure that it is accurate, complete, and that its collection is in compliance with the protocol. There will also be a continual assessment of the risks and benefits.

Furthermore, Case report forms will be generated for each subject and completed by the investigator or study coordinator. The investigator or study coordinator will countersign each form. After the case report forms for a visit are completed, the research coordinator will enter a limited set of data into a data management system. Original case report forms will be securely maintained at the clinical sites. Completed copies of the case report forms will be sent to the research coordinator where they will be stored on the Shared "S" Drive. Subjects will be asked to report any adverse events to the study coordinator or physician. All adverse events will be reported on a standardized form that will elicit the number and specify the type of tests used, therapy (or therapies) used, and clinical visits (office, ER and hospitalization) required until the event is resolved.

DEVICE DESCRIPTION:

The RELIEF™ Ureteral Stent assembly consists of four components (Ref: Figure 2): Proximal ureteral stent body (A) with a proximal coil that is placed in the kidney and lumen that extends into the ureter, constructed of commonly used stent materials; Tether (B) consisting of suture material that is secured to the proximal and distal ends; Distal coil (C) comprised of a solid polymeric coil with a "pigtail" geometry that floats in the bladder; Pull-out suture (D) secured to the distal coil and that allows for retrieval of the stent. The pull-out suture will not be used in the current study per recommendation of our UH Endourology providers, who are involved in the study, as it might lead to urethral irritation, which might conflict the results of the study.

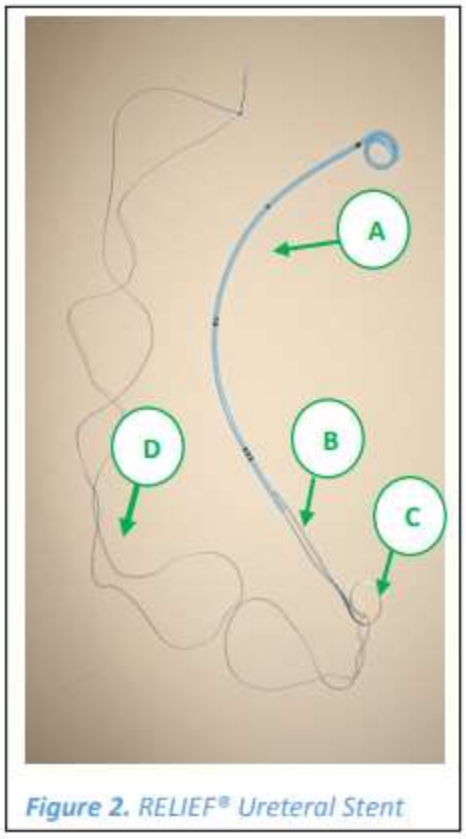
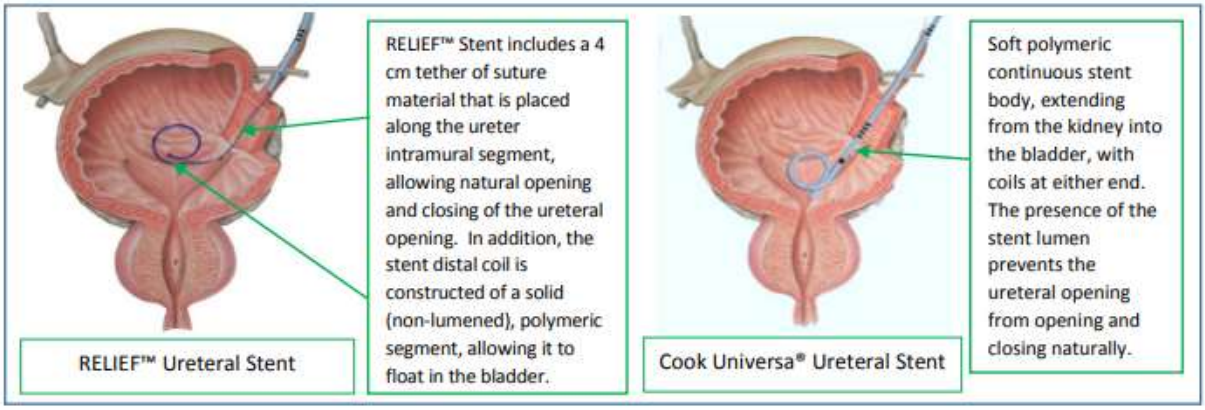


Figure 2. RELIEF® Ureteral Stent

The RELIEF™ Ureteral Stent is classified by FDA as a Class II device, requiring a 510(k) pre-market clearance before sale. Based on a review of commercially-available ureteral stents, the Cook Universa® Firm Ureteral Stent with Hydrophilic Coating and Monofilament Tether (https://www.cookmedical.com/products/uro_ufh2_webds/) has been selected as the predicate device for the RELIEF™ Ureteral Stent 510(k) submission (Figure 3).

Figure 3. RELIEF™ Ureteral Stent and its Predicate Device, Cook Universa® Firm Ureteral Stent with Hydrophilic Coating and Monofilament Tether



The Relief Stent has been designed and developed and manufactured with guidance from North Coast Medical Development LLC, Concord Twp. Ohio and Medical Murray LLC. North Barrington, Illinois. The

Relief Stent device manufacturing for use in the investigation will be implemented in accordance with all parts of Investigational Device Exemption FDA 21CFR- Part 812. The device is designed, developed and manufactured in accordance with FDA QSR 21CFR- Part 820 subpart C Design Controls of the Quality System Regulation and relevant sections of FDA QSR 21CFRPart 820 Quality System Regulation. In addition, Medical Murray LLC is certified to ISO 13485:2003 for design and manufacturing of Medical Devices. The device is manufactured, assembled, packaged and labelled using conventional methods and hand assembly techniques. The ethylene oxide gas sterilization of the devices will be completed by a certified contract sterilization company.

References

1- Chew, B.H., B.E. Knudsen, and J.D. Denstedt, The use of stents in contemporary urology. Current opinion in urology, 2004. 14(2): p. 111-115.
2- Joshi, H., et al., Characterization of urinary symptoms in patients with ureteral stents. Urology, 2002. 59(4): p. 511-516.
3- Chambade, D., et al., Study of the safety of double J ureteric stents. Progres en urologie: journal de l'Association francaise d'urologie et de la Societe francaise d'urologie, 2006. 16(4): p. 445-449.
4- Shao, Y., et al., The influence of ureteral stent on renal pelvic pressure in vivo. Urological research, 2009. 37(4): p. 221-225.
5- Giannarini, G., et al., Predictors of morbidity in patients with indwelling ureteric stents: results of a prospective study using the validated Ureteric Stent Symptoms Questionnaire. BJU international, 2011. 107(4): p. 648-654.
6- Krebs, A., et al., The 'buoy'stent: evaluation of a prototype indwelling ureteric stent in a porcine model. BJU international, 2009. 104(1): p. 88-92.
7- CDRH, F. Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors. Significant Risk and Nonsignificant Risk Medical Device Studies 2017 [cited 2017 3-22]; Available from: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126418.pdf.
8- Cookmedical. Instructions for Use Universa Cook Stents. [Pdf] 2017 [cited 2017 03-20]; Available from: https://www.cookmedical.com/data/IFU_PDF/T_USS_REV3.PDF.
9- FDA, D.O.H.H.S. Universa Firm Ureteral Stents and Stent Sets 510(k) notification. [Pdf] 2017 [cited 2017 03-22]; Available from: http://www.accessdata.fda.gov/cdrh_docs/pdf16/K161236.pdf.
10- Cookmedical. Universa® URETERAL STENT SET. 2017 [cited 2017 03-22]; Available from: https://www.cookmedical.com/data/resources/URO-BM-UNISTB-EN-201402-M3.pdf