Two single arm, multicentre unblinded first-in-human trials, including 2 phases and a qualitative substudy investigating a novel ureteric stent in Kidney stone patients and Oncology patients to determine the reduction of encrustation, biofilm deposition and complications compared to a conventional JJ stent

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Clinical Investigation Plan Information

This Clinical Investigation Plan (CIP) describes the CASSETTE trial and provides information about procedures for entering participants. The CIP should not be used as a guide for the treatment of other non-trial participants; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the trial, but sites entering participants for the first time are advised to contact Southampton Clinical Trials Unit to confirm they have the most recent version.

Compliance

This trial will be conducted in compliance with the approved CIP and will adhere to the principles outlined in the Medical Device Regulations 2002 (SI 2002 No.618), any subsequent amendments of the clinical trial regulations, GCP guidelines, ISO 14155:2020, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

The following terminology is used in this trial, with ISO 14155 equivalent in brackets: Chief Investigator (Principal Investigator); Sponsor (Sponsor – Legal Entity); Funder (Sponsor – Funding Entity)

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LIST OF ABBREVIATIONS

AE	Adverse Event
AMR	Antimicrobial resistance
E&B	Encrustation and biofilm formation
EQ 5D	Euroqol 5 dimensions (Quality of Life questionnaire)
CI	Chief Investigator
CIP	Clinical Investigation Plan
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DMEC	Data Monitoring and Ethics Committee
DMP	Data Management Plan
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
IDMC	Independent Data Monitoring Committee
IB	Investigators Brochure
IFU	Instructions for Use
ISF	Investigator Site File
ITU	Intensive Therapy Unit
IV	Intravenous
MHRA	Medicines and Healthcare products Regulatory Agency
NCI	National Cancer Institute
PCNL	Percutaneous Nephrolithotomy
PE	Pulmonary Embolism
PI	Principal Investigator
PIS	Participant Information Sheet
QOL	Quality of life
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCTU	Southampton Clinical Trials Unit
SEM/EDX imaging	Scanning Electron Microscopy (SEM) with Energy Dispersive X-Ray Analysis (EDX)
TMF	Trial Master File
TMG	Trial Management Group
USI-QoL	Urinary Stones and Intervention Quality of Life Measure
USSQ	Ureteric stent symptom questionnaire
UTI	Urinary tract infection

KEYWORDS
Novel ureteric stent, First in human, Medical Device, Quality of Life

CLINICAL INVESTIGATION SYNOPSIS

Short title:	CASSETTE
Full title:	Two single arm, multicentre unblinded first-in-human trials, including 2 phases and a qualitative substudy investigating a novel ureteric stent in Kidney stone and Oncology patients to determine the reduction of encrustation, biofilm deposition and complications compared to a conventional JJ stent

Phase:	First-in-human
Population:	Patients (male & female) aged 18 years or older with kidney stones or abdominal cancers, with previous experience of ureteric stents and clinical indication for ureteric stents. Inclusion criteria: 1. Aged 18 years or over 2. Ureteric stents clinically indicated either due to kidney stones or abdominal/pelvic cancers compressing ureters 3. Previous experience with ureteric stents 4. Awaiting insertion/replacement of stents 5. Able to give informed consent 6. Ability to interact with written and online study documentation 7. Sufficient English to complete study documentations and questionnaires Exclusion criteria: 8. Expected survival <4months 9. Unfit for stent insertion 10. Unable to comply with study processes 11. Pregnancy 12. Planned stent removal is not at the same hospital as the stent insertion
Primary Objective:	To determine rates of stent failure
Secondary Objective:	To assess extent of encrustation and biofilm (E&B) To determine whether the novel stent leads to better clinical outcomes To assess impact of the novel stent on quality of life To understand patient experience in having the novel stent in place To understand healthcare professional experience and to understand the acceptability of the novel ureteric stent
Tertiary Objective	N/A
Rationale:	Urological stents and catheters often lead to inflammation, causing pain and infection in the urinary tract[9]. Moreover, 80% of stents are associated with pain, negatively impacting on QoL [10] and mental health. Offering novel designs with significantly lower E&B should lead to a reduction in UTIs and improves QoL. Reducing hospital admissions (from 3 to 1 per patient, annually) would free >100,000 bed-nights, allowing the elderly to regain independence. Our proposed research could have a significant impact towards fulfilling the 'healthy-ageing' Grand Challenge. Additionally, if the novel ureteric stent reduces prevalence of infections, it would support reduction of antibiotic prescriptions contributing to the antimicrobial resistance challenge.
Clinical Investigation Design:	Two single arm, multicentre unblinded first-in-human trials, including 2 phases and a qualitative substudy

Duration of the clinical investigation:	Expected total duration = 16 months Recruitment duration = 12 months Intervention duration for Kidney cohort = <4 weeks Intervention duration for Oncology cohort = ~25 weeks Follow up duration for both cohorts = 2-3 weeks
Sample size:	Novel ureteric stent insertion: 50 patients (25 kidney stone patients, 25 oncology patients) Patients Interviews: Until sample saturation (expected 30 – 40) Practitioner Interviews: Until sample saturation (expected up to 15)

URL for Database:	https://www.imedidata.com
URL for randomisation:	Not applicable

Primary Trial Endpoints:	Stent failure, defined as any of a): a change earlier than planned (oncology only); b) need for additional surgical or radiological intervention; c): kidney failure and/or worsening hydronephrosis on imaging
Secondary Trial Endpoints:	Dwell time Individual components of the primary outcome Urinary symptoms Infections (antibiotic use, re-admission, urosepsis, ITU, and death) Cell culturing (CFU counts) Interviews conducted with participants; interviews conducted with clinicians
Exploratory Endpoint:	Weight of stent pre-to post insertion Flow Imaging (selected samples – when needed)
Total Number of Sites:	2 NHS Trusts in England

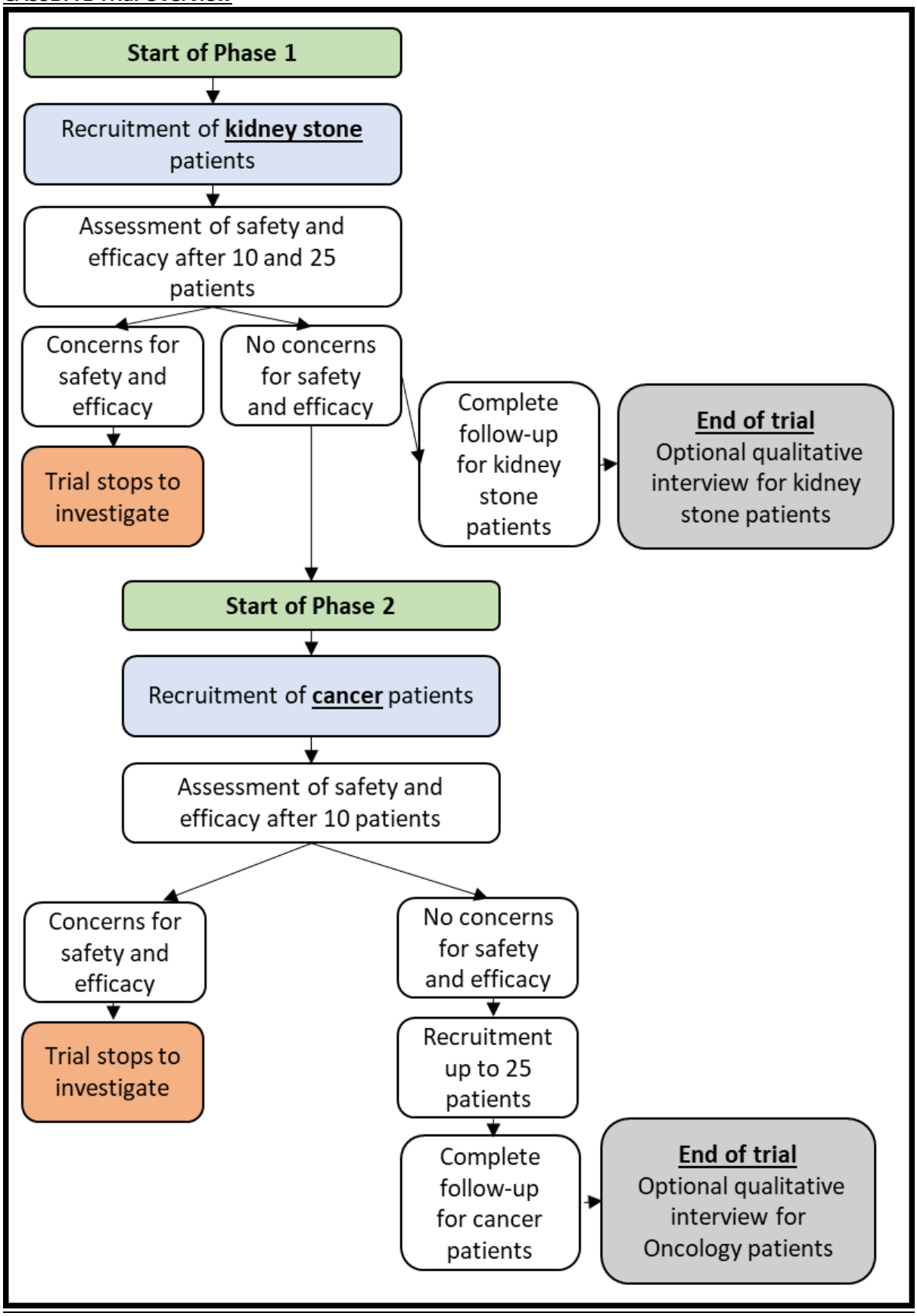
IDENTIFICATION AND DESCRIPTION OF THE INVESTIGATIONAL DEVICE

Summary description of the investigational device:	The investigational device (herein referred to as "*Novel Ureteric Stent")* consists of a ureteric stent and standard of care stent pusher. The stent is a disposable, sterile, single use device that allows internal drainage of urine from the kidney to the bladder. Details of the investigational device are contained (or referenced) within the Investigator's Brochure (IB).
Manufacturer details:	The manufacturer of the device is University of Southampton Research and Innovation Services. Research and Innovation Services University of Southampton Building 37 Highfield Campus Southampton SO17 1BJ Tel: +44(0)23 80 595058 Web: https://www.southampton.ac.uk/research/ris.page
Identification of device:	Novel ureteric stents (+ a pusher) individually packaged and labelled with manufacturing batch numbers and unique individual identifiers per stent

Traceability of device:	Each novel ureteric stent will be provided in individual packaging. The label on the packaging will contain a batch/LOT number as well as a unique identifier per stent. The unique identifier will be recorded in the patient medical notes as well as on the trial database, allowing for traceability of each individual stent. Full accountability of the investigational devices is detailed further in Cassette Medical Device Accountability Document
Purpose of the device:	To facilitate continuous drainage of urine from the kidney to the bladder. Suitable for short to long term use in patients with compromised flow in the ureter
Description of device in contact with tissues of body fluids:	The *Novel Ureteric Stent* (for clinical investigation sponsored by the University of Southampton) contains a ureteric stent and stent pusher. The stent is a flexible polymeric disposable tube with series of holes, tapered tip and end tails (also known as j-tails), sterile, single use device that allows internal drainage of the urine from the kidney to the bladder
Training and experience:	Detailed in section 4.4
Medical or surgical procedures:	Detailed in section 4.5
References to Investigators Brochure (IB) and Instructions for Use (IFU):	Novel Ureteric Stent – Investigator Brochure Novel Ureteric Stent - Instructions for Use

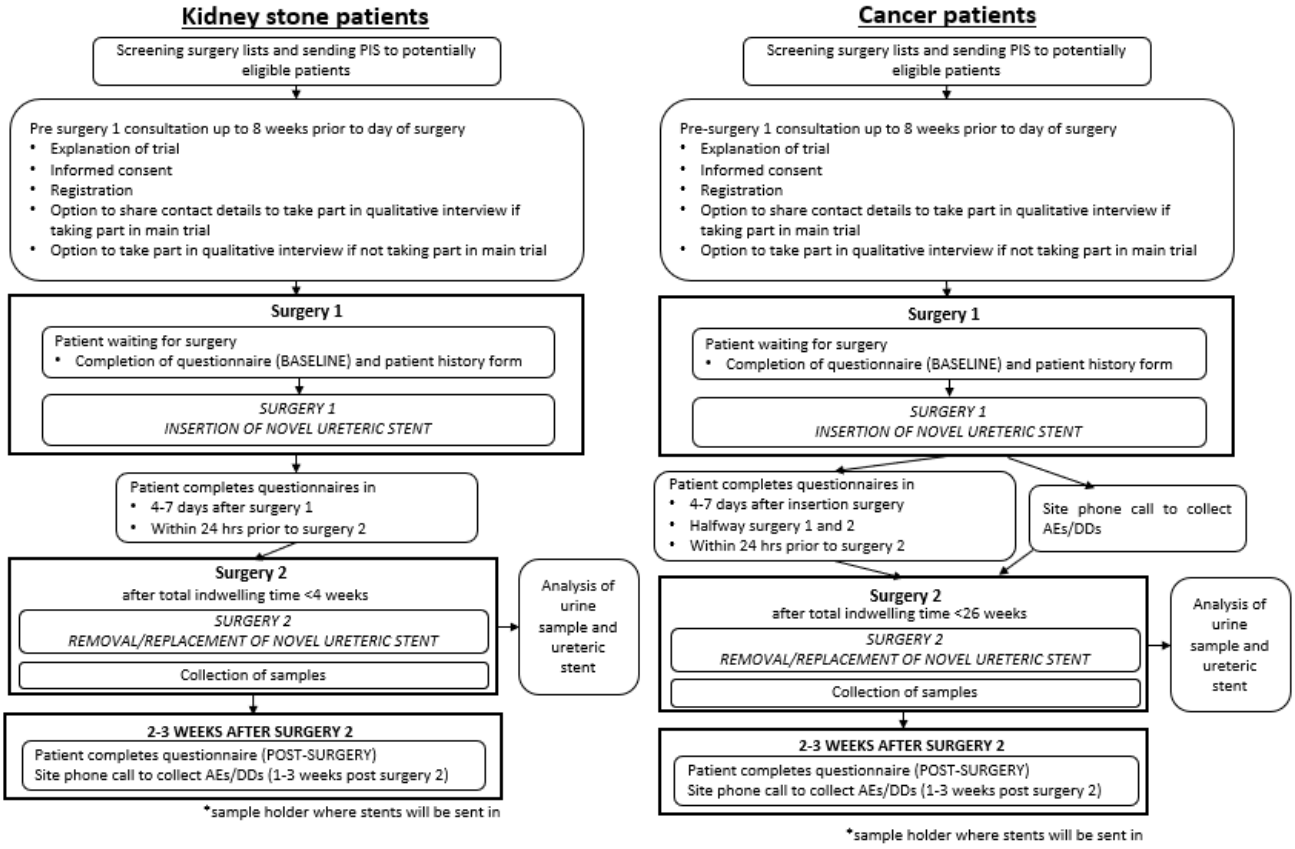
TRIAL SCHEMA

CASSETTE Trial Overview



TRIAL SCHEMA

CASSETTE patient pathway



SCHEDULE OF OBSERVATIONS AND PROCEDURES

KIDNEY STONE (KS) PATIENTS

	Responsibility*1	Timepoint						
		Screening	**Surgery 1**	**4-7 days post-Surgery 1**	**Within 24 hrs prior to surgery 2**	**Surgery 2**	**2-3 weeks post-Surgery 2**	**Qualitative interview (optional timepoint)**
		(Day 0) Up to 8 weeks before surgery	**Day of novel ureteric stent insertion**	**4-7 days post novel ureteric stent insertion**	**Within 24 hours prior to the novel ureteric stent removal**	**Day of removal of novel ureteric stent**	**2-3 weeks post novel ureteric stent removal**	**Within first month of stent removal for participants (Up to 1 month from recruitment end for clinicians)**
Screening of surgery lists and sending PIS to potentially eligible patients	Site	x						
Informed Consent*2	Site	x	x					
Eligibility evaluation*2	Site	x	x					
Medical History (Clinical team may review medical history to check eligibility criteria)	Site	x	x					
Check for Adverse Events/Device Deficiencies)	Site		x			x	x*3	x
Registration*2	Site	x	x					
Physical Exam*2	Site	x	x					
KS Patient Questionnaire – BASELINE	Patient		x					
KS Patient In Situ Questionnaire	Patient			x	x			
KS Patient Questionnaire (Post-surgery)	Patient						x	
Investigational device insertion	Study doctor		x					
Investigational device removal	Study doctor					x		
Sample collection (urine and removed novel ureteric stent)	Site					x		
Laboratory Tests (pre-op anaesthetic tests) – as required by the clinical team*4	Site	x						

Endpoint analysis – weighing, cell culture, imaging	Microbiology research lab/imaging unit					x		
Endpoint analysis - Flow rate	Bioengineering lab					x		
Safety blood test (eGFR, Creatinine) – (when clinically needed) *[4]	Site					x		
Pregnancy Test*[4]	Site		x			x		
Qualitative Interview (optional)	Qualitative researcher							x

NB: The Participant/legal representative is free to withdraw consent at any time without providing a reason. When withdrawn, the participant will continue to receive standard clinical care. Follow up data will continue to be collected (unless the participant/legal representative has specifically stated that they do not want this to happen).

*[1] Tasks may only be performed by those suitably trained and authorised (documented on the study delegation log) to do so. Eligibility (see section 5) and assessment of safety events (see section 7) must be performed by a **medically qualified doctor**

*[2] Can either be completed at the screening visit or on day of surgery 1 (not required at both timepoints) – but informed consent must be obtained before all other trial procedures

*[3] Call to participant to check AE/DDs (1-3 weeks post-surgery 2)

*[4] These are standard of care tests which may be performed as required at the request of the clinical team. This will only be entered in the trial database if clinically relevant.

ONCOLOGY (Onc) PATIENTS

	Responsibility*1	Timepoint							
		Screening	**Surgery 1**	**4-7 days post Surgery 1**	**Between Surgery 1 & 2**	**Within 24 hrs prior to surgery 2**	**Surgery 2**	**2-3 weeks post Surgery 2**	**Qualitative interview (optional timepoint)**
		(Day 0) Up to 8 weeks before surgery	**Day of novel ureteric stent insertion**	**4-7 days post novel ureteric stent insertion**	**Halfway between surgery 1 and surgery 2 (midpoint to be based on planned removal/replacement date +/- 1 week)**	**Within 24 hours prior to the novel ureteric stent removal**	**Day of removal of novel ureteric stent**	**2-3 weeks post novel ureteric stent removal**	**Within first month of stent removal for participants (Up to 1 month from recruitment end for clinicians)**
Screening of surgery lists and sending PIS to potentially eligible patients	Site	x							
Informed Consent*2	Site		x						
Eligibility evaluation	Site	x							
Medical History (Clinical team may review medical history to check eligibility criteria)	Site	x	x						
Check for Adverse Events/Device Deficiencies	Site		x		x*3		x	x*3	X
Registration*2	Site	x	x						
Physical Exam*2	Site	x	x						
Onc Patient Questionnaire - BASELINE	Patient		x						
Onc Patient In Situ Questionnaire	Patient			x	x	x			
Onc Patient Questionnaire (Post-surgery)	Patient							x	
Investigational device insertion	Study doctor		x						
Investigational device removal	Study doctor					x			
Sample collection (urine and removed novel ureteric stent)	Site					x			

Laboratory Tests (pre-op anaesthetic tests) – as required by the clinical team*[4]	Site	x							
Endpoint analysis – weighing, cell culture, imaging	Microbiology research lab/imaging unit						x		
Endpoint analysis - Flow rate	Bioengineering lab						x		
Safety blood test (eGFR, Creatinine) – (when clinically needed) *[4]	Site						x		
Pregnancy Test*[4]	Site		x				x		
Qualitative Interview (Optional)	Qualitative researcher								x

NB: The Participant/legal representative is free to withdraw consent at any time without providing a reason. When withdrawn, the participant will continue to receive standard clinical care. Follow up data will continue to be collected (unless the participant/legal representative has specifically stated that they do not want this to happen).

*[1] Tasks may only be performed by those suitably trained and authorised (documented on the study delegation log) to do so. Eligibility (see section 5) and assessment of safety events (see section 7) must be performed by a **medically qualified doctor**

*[2] Can either be completed at the screening visit or on day of surgery 1 (not required at both timepoints) – but informed consent must be obtained before all other trial procedures

*[3] Call to participant to check AE/DDs midway between surgery 1 and surgery 2 and 1-3 weeks post-surgery 2

*[4] These are standard of care tests which may be performed as required at the request of the clinical team. This will only be entered in the trial database if clinically relevant.

1 INTRODUCTION

1.1 BACKGROUND

Ureteric stents and catheters are deployed clinically as temporary measures to restore urinary drainage, in patients with kidney stones, tumours and strictures. Prevalence of these increases with age [1]–[4]. Device-associated encrustation and biofilm formation (E&B) are key complications, leading to urinary tract infections (UTIs) in >90% of stents [5], causing stent blockage and favouring development of antibiotic resistance.

UTIs are a significant cause of morbidity, especially among the elderly population, with 4,835 deaths in England and Wales reported in 2012 [6]. The National Institute for Health Research (NIHR, 2016) reported that 1-3% of all primary care consultations concern UTI-related symptoms, leading to 13.7% of antibiotic prescriptions globally. The report also revealed that >92m people globally are diagnosed with UTIs annually [7].

Urological device-associated infections significantly compromise patient' quality of life and the effectiveness of services, imposing a £2.5b annual burden on the NHS [8]. Patients' exposure to hospital environment and general anaesthetic use impact on Quality-of-Life (QoL), resulting in unnecessary hospital bed-nights. We have developed a novel urological stent associated with significantly reduced particle deposition, potentially extending the stent's lifetime, resulting in reduced hospitalisation and improved QoL.

Urological stents and catheters often lead to inflammation, causing pain and infection in the urinary tract [7]. Moreover, 80% of stents are associated with pain, negatively impacting on QoL [9] and mental health. Offering novel designs with significantly lower E&B leads to a reduction in UTIs and improves QoL. Reducing hospital admissions (from 3 to 1 per patient, annually) would free >100,000 bed-nights, allowing the elderly to regain independence. Our proposed research could have a significant impact towards fulfilling the 'healthy ageing' Grand Challenge. Additionally, the novel stent reduces prevalence of infections and therefore, of antibiotic prescriptions contributing to the Global Antimicrobial Resistance (AMR) challenge.

Considering only onco-urological patients, >30,000 stents are inserted every year across 200 NHS units. Due to stent failures, each patient undergoes 3 to 6 replacements, resulting in >90,000 stent replacements. Under the current tariff-based system, hospitals are paid for each intervention, costing the NHS >£3,500, bringing the total cost of replacements to ~£315m annually. Unnecessary replacements increase the number of bed-nights and use of anaesthetics. A longer-lasting stent means that each patient comes to the hospital ideally only once, reducing their exposure to the hospital environment and anaesthetic-associated risks. Additionally, under the current model hospitals would improve their quality of service and save at least 2 bed-nights per patient. The NHS is moving towards a "block contract" model, meaning that hospitals will receive a lump sum for the year, and they'll regularly monitor budgets and improve cost efficiency where possible. Improved stents will allow the same urology budget to deliver more healthcare, reducing theatre time for stent insertion and replacement. Our innovative stent design offers a potential annual saving of >£210m for the NHS, allowing hospitals to reallocate their resources. Today E&B is still a major determinant of stent failure and associated side effects. We aim to address this challenge through our novel stent, and if equivalent safety and improved efficacy are demonstrated, anticipate market launch via third-party suppliers 2-3 years post project.

Solutions to break this pathway (stent presence leading to inflammation, pain and infection) have been developed, including stent construction materials (e.g. metallic alloys, polymers, biodegradable and drug-eluting materials), stent coatings (e.g. heparin, chitosan, hydrogel, carbon) and alternative stent shapes (e.g. double-J, loop, mesh, string, expandable), to improve the efficacy and safety of stents [10]–[13]. Despite all these advances, there is still a significant prevalence of E&B [14]–[16]. This is also due to the lack of studies correlating fluid dynamic metrics with deposition of particles causing E&B. The lead applicant's PhD

investigated the mechanisms of particle deposition in urological stents, and successfully determined fluid dynamic parameters governing particle deposition on ureteric stents and catheters. His research led to developing a stent with specially shaped side-holes that prevent stagnation points (i.e., areas of low flow that cause particles to settle and E&B). These developments demonstrated >80% reduction in particle deposition at side-holes, in-vitro [17], [18]. Their innovative architecture can be implemented on stents and catheters. The technology, including the stent design and manufacturing process, is protectable – Patent# WO2019048860A1, WIPO(PCT). These results were further validated in an animal study (6 pigs: 3 novel-design stents vs 3 conventional-design stents for a 4-week period) at Stone Centre at Vancouver General Hospital (VGH), a centre of excellence in animal studies on urological products. The study (available upon request) concluded that the functionality of stents with novel side-holes is the same as that of standard stents in terms of safety. Specifically, the novel stent does not result in increased risk of irritation, inflammation and hydronephrosis [19]. Furthermore, Scanning Electron Microscopy (SEM) with Energy Dispersive X-Ray Analysis (SEM/EDX) imaging showed that the novel design decreased the build-up of particles on the stent surface. Thus, it demonstrated significant potential for the new side-hole configuration to change patterns of particle deposition on the stent's surface, decreasing encrustation.

1.2 BENEFITS AND RISKS OF THE INVESTIGATIONAL DEVICE, CLINICAL PROCEDURE, AND CLINICAL INVESTIGATION

1.2.1 Anticipated clinical benefits

This study provides participants an opportunity to benefit from the novel ureteric stent which should be less prone to blockages. Anticipated clinical benefits relating to reductions in UTIs, pain, number of surgeries and exposure to possible hospital-acquired infections are described throughout section 1.1.

1.2.2 Anticipated adverse device effects

- During insertion - difficulty advancing because of stent buckling on the side hole. If this happens, it can increase the operation time by 5 mins.

- During removal - stent fracturing on the side holes, which could increase the chance of needing a surgery (ureteroscopy or even a Percutaneous Nephrolithotomy (PCNL) or a second operation).

- Encrustation and biofilm formation (E&B) leading to failure to drain**.** Clinical judgement will be required for each incidence, to determine whether this is the outcome of the new design or not.

- Functional challenges (failing to drain or it is not doing what it is supposed to do). Evidenced by change earlier than planned (for oncology participants), need for additional surgical or radiology intervention (could be anything beyond the planned normal) or "kidney failure" (evidenced by AKI (Acute kidney injury) on blood tests (eGFR / Creatine kidney functioning tests) and/or WORSENING of hydronephrosis on Imaging oncology).

1.2.3 Risks associated with participation in the clinical investigation

Risks associated with participation in the clinical investigation are not expected to be beyond those associated with standard of care for stent insertion in these patient groups. Risks associated with the device are detailed in section 1.2.2 as expected device effects. Risks relating to patient safety are detailed in the Investigators' Brochure, and are summarised below:

- Cystitis/UTI (urinary tract infection) and associated symptoms
- Stent bother
- Haematuria
- Loin pain

All risks associated with participation in the clinical investigation have been assessed and documented in the Trial Risk Assessment as appropriate.

1.2.4 Possible interactions with concomitant medical treatments as considered under the risk analysis

The novel ureteric stent is compatible with (and would not require any deviation from the routine plan for) all forms of imaging, any medication, and any surgical intervention.

1.2.5 Steps that will be taken to control or mitigate the risks

- If it is difficult to advance because of stent buckling on the side hole, then a stiffer wire is to be used (as is standard practice) or stent will be changed to a different one (either new investigational device or standard stent, as decided by clinician) to reduce the risk. This, if happens, can increase the operation time by 5 mins.
- If the participant experiences functional challenges with the stent (the stent failing to drain or work as expected), and required additional intervention (i.e. draining kidney by alternative means e.g. nephrostomy, alternative stent), then pause this participant's involvement (as decided by clinician) and analyse/investigate as per stop/go criteria (see section 3.1)
- Due to the novel nature of the investigational device, stopping criteria (see section 3.1) have been included in the trial design to monitor and assess the events listed in section 1.2.2

1.2.6 Rationale for benefit-risk ratio

A previous study has shown that that the functionality of stents with novel side-holes is the same as that of standard stents in terms of safety. The novel stent does not result in increased risk of irritation, inflammation and hydronephrosis [18]. Furthermore, SEM/EDX imaging showed that the novel design decreased the build-up of particles on the stent surface and inside its side-holes. Thus, it demonstrated significant potential for the new side hole configuration to change patterns of crystal deposition on the stent's surface, decreasing encrustation.

2 TRIAL OBJECTIVES AND ENDPOINTS

2.1 PURPOSE OF THE CLINICAL INVESTIGATION

We have identified a reason behind failure of currently used devices and have developed new patented stents preventing blockage by crystals and bacterial build-up. To date, we have conducted laboratory experiments and animal testing, and aim to perform a first in human trial to primarily assess failure rates and determine whether it is suitable to progress the development and testing of the stent further. We will further explore outcomes related to:

1. Encrustation and biofilm formation
2. Stent lifetime
3. Quality of life
4. Infection

2.2 PRIMARY TRIAL OBJECTIVE AND ENDPOINT

The primary endpoint is stent failure, defined as any of:

a) a stent change earlier than planned (oncology only);
b) need for stent related additional surgical or radiological intervention;
c) kidney failure and/or worsening hydronephrosis.

No intercurrent events (events that would affect the collection or interpretation of stent failure data) are thought likely to occur.

2.3 SECONDARY TRIAL OBJECTIVE AND ENDPOINT

The secondary endpoint is to assess extent of encrustation and biofilm (E&B) via:

a) Cell culturing (CFU counts per ml per bacterial microorganism)
b) Dwell time
c) Imaging (EDIC microscopy, selected samples – when needed)

2.4 EXPLORATORY TRIAL OBJECTIVE AND ENDPOINT

The exploratory endpoint is to assess extent of encrustation and biofilm (E&B) via:

a) Weight: Post-removal, stents will be packaged and sent to the University of Southampton Microbiology Research Laboratory for weighing.
b) Flow study (pressure value): A section of the retrieved stent will be used for flow study. The part will be placed into a larger diameter tube. DI water/Saline is injected using a pump into the inlet of the external tube and pressure sensor is connected to the inlet tube. Pressure readings will be captured per stent.
c) Imaging (SEM microscopy, selected samples – when needed)

2.5 TABLE OF ENDPOINT/OUTCOMES

	Objective	Outcome Measures	Summary method(s)
Primary	To determine rates of stent failure	Stent failure, defined as any of: a) a stent change earlier than planned (oncology only); b) need for stent related additional surgical or radiological intervention; c) kidney failure (evidenced by acute kidney injury (AKI) on blood tests (eGFR or creatinine kidney function tests) and/or worsening hydronephrosis on imaging	Frequency and percentage of people experiencing any stent failure
Secondary	To assess extent of encrustation and biofilm (E&B)	• Cell culturing (CFU counts per ml per bacterial microorganism) • Dwell time • Imaging (selected samples of stents will be examined using non-contact, non-destructive episcopic-differential-interference-contrast (EDIC) microscopy allowing imaging of the surface with the biofilm in-	• Mean and standard deviation or median • Absolute value (Days)

		situ and colonisation by bacteria – when needed).	
	To determine whether the novel stent leads to better clinical outcomes	• Individual component of the primary outcome • Urinary symptoms • Infections	• As per primary outcome • Frequency and percentage of participants experiencing each symptom • Frequency and percentage of people with antibiotic • use, readmission, urosepsis, ITU, death; number of infections per unit of time stent is in use
	To assess impact of the novel ureteric stent on quality of life	Questionnaires at: • Baseline • While stent is in situ • Post-surgery	Appropriate descriptive summaries (e.g., median and quartiles) per timepoint
	To understand patient experience in having the novel ureteric stent inserted and reason for participation in the trial	30–45-minute Qualitative interviews with Oncology and Kidney stone cohorts	An inductive thematic analysis of interview transcripts
Exploratory	To assess extent of encrustation and biofilm (E&B)	• Weight: Stents will be weighed post-removal upon arrival at the microbiology lab • Flow study (pressure value): A section of the retrieved stent will be used for flow study. The part will be placed into a larger diameter tube. DI water/Saline is injected using a pump into the inlet of the external tube and pressure sensor is connected to the inlet tube. Pressure readings will be captured per stent.	Mean and standard deviation or median and quartiles of weights pre- and post-insertion Mean and standard deviation or median and quartiles of pressure readings

		• Imaging (selected samples of stents will be examined using non-contact, non-destructive SEM (scanning-electron-microscopy) allowing imaging of the surface with the biofilm in-situ and colonisation by bacteria – when needed).	

3 OVERALL TRIAL DESIGN

Two single-arm, multicentre, unblinded, first-in-human trials to investigate a novel ureteric stent in 1) patients with kidney stones and 2) oncology patients. The two separate arms will run simultaneously, with a stopping point to assess the safety of the stent in the Kidney Stone cohort, before the Oncology cohort recruitment commences. This is an early phase trial to assess whether this stent can be inserted and does not have discernible difference in failure or symptoms in patients who have "lived experience" with a previous (market standard) ureteric stent. Each single-arm trial runs in two phases, with a pause to assess safety, and recruitment to the oncology cohort will only occur following safety review for the kidney stone cohort. A qualitative sub study will also be carried out across the two arms. A control group is not included as the aim of the trial is to generate initial first-in-human data to support further development and testing of the novel ureteric stent. Data from a (partly) contemporaneous study (UPPEUS) will be used to support this decision. The design is aligned with the IDEAL framework (designed for novel surgical interventions), and specifically phase 2a of the development process [20]

Kidney stone patients and oncology patients admitted to either the University Hospital Southampton (UHS) or University College London Hospital (UCLH) for management of kidney stones or for the management of urine drainage in ureter will have a novel ureteric stent instead of a conventional stent. The novel ureteric stent will be removed or replaced within 4 weeks (kidney stone patients) or ~25 weeks (oncology patients). Recruitment to the cohort of oncology patients will only commence after a safety review of 10 kidney stone patients have taken place.

The Kidney stone patients will be assessed for safety signals after 10 and 25 patients have had the novel ureteric stents removed (<4 weeks after insertion). Recruitment will continue while the analysis of the first 10 patients takes place. Stopping rules after 10 and 25 patients are summarised in Table 1 below.

3.1 STOPPING CRITERIA

Table 1 - Stopping rules for kidney stone patients

Criteria / Event	Criteria (1) Rule following 10 patients	Criteria (2) Rule following 25 patients
Insertion (not severe) – clinical judgement: If it is difficult to advance because of stent buckling on the side hole, then a stiffer wire is used as standard method or stent will be changed to • **Alternative** stent (same make / design but different size French calibre or length) E.g. novel stent 6Fr / 22cm changed to a novel stent 8Fr 24cm (Not a STOP) • **Different** Stent (a different make/design of stent regardless of calibre or length) E.g. novel stent 6Fr / 22cm changed to a Boston 6Fr / 22cm (It is a STOP)	Stop/pause and investigation if >4 patients affected	Stop/pause and investigation if >10 patients affected in total

to reduce the risk. This, if happens, can increase the operation time by approximately 5 mins.		
Removal (could be severe) – clinical judgement: if stent fractures on the side holes, which could increase the chance of needing a surgery (ureteroscopy or even a Percutaneous Nephrolithotomy (PCNL) or a second operation). This is the main reason for pausing the trial until investigation of whether the stent was the cause.	Stop/pause and investigation if >2 patients affected	Stop/pause and investigation if >5 patients affected
Removal of stent <7 days of insertion due to severe infection, overwhelming symptoms, or failure to drain (clinical judgment)	Stop/pause if >4 patients	Stop/pause if >4 patients

If no safety and efficacy concerns are found in the kidney stone patient group (following criteria 1), recruitment of cancer patients admitted to either the University College London Hospital (UCLH) or University Hospital Southampton (UHS) for management of urine drainage in ureter will commence. The cancer patient group will also be assessed for safety signals one week after the 10th patient has had their stent inserted. Another safety assessment of the same cohort will also take place once a further 15 patients have been recruited (25 in total). Recruitment will not be paused during this time.

Table 2 - Stopping rules for cancer patients

Criteria / Event	Rule up to the first 10 patients	Rule up to the next 15 patients (ie. 25 in total)
Insertion (not severe) – clinical judgement: If it is difficult to advance because of stent buckling on the side hole, then a stiffer wire is used as standard method or stent will be changed to • **Alternative** stent (same make / design but different size French calibre or length) Eg Modified stent 6Fr / 22cm changed to a modified stent 8Fr 24cm (Not a STOP) • **Different** Stent (a different make/design of stent regardless of calibre or length) Eg Modified stent 6Fr / 22cm changed to a Boston 6Fr / 22cm (It is a STOP) to reduce the risk. This, if happens, can increase the operation time by approximately 5 mins.	Stop/pause and investigation if >4 patients affected	Stop/pause and investigation if >10 patients affected in total
Removal (could be severe) – clinical judgement: if stent fractures on the side holes, which could increase the chance of needing a surgery (ureteroscopy or even a Percutaneous Nephrolithotomy (PCNL) or a second operation). This is the main reason for pausing the trail until investigation of whether the stent was the cause.	Stop/pause and investigation if >2 patients affected	Stop/pause and investigation if >5 patients affected in total
Removal of stent <7 days of insertion due to severe infection, overwhelming symptoms, or failure to drain (clinical judgment)	Stop/pause if >4 patients	Stop/pause if >10 patients in total

At least 30-40 participants (until sample saturation), who have the novel ureteric stent inserted, at UHS and UCLH, will be invited by letter or email (by the qualitative researcher at the University of Southampton) to an interview (up to 45 minutes by telephone or video call). Patients who did not wish to have the novel ureteric stent will have the option to provide informed consent to take part in qualitative interviews sharing their experiences and reasons for not opting to have the novel ureteric stent. It would be relevant to

interview people who did not want to take part, in order better to understand how we can improve the design to make it easier to recruit to a future larger scale study. All participants will be given a copy of the participant information sheet about these interviews.

The qualitative researcher (at the University of Southampton) will contact the patients who consented to their contact details being shared to discuss any potential questions and to arrange a time to speak with them by telephone and/or video call.

4 INVESTIGATIONAL DEVICE(S) AND COMPARATOR

4.1 EXPOSURE TO INVESTIGATIONAL DEVICE

The ureteric stent is an indwelling device, which is implanted into the urinary tract. The duration of exposure will be dependent on patient cohort and clinical necessity (short dwell time e.g. kidney stone patients OR long dwell time e.g. oncology patients). Clinician will handle the stent as per usual stent insertion and removal/replacement processes.

4.2 OTHER DEVICES/MEDICATION TO BE USED DURING THE CLINICAL INVESTIGATION

As part of the standard procedure clinician will also use lubricating gel to facilitate passage of the cystoscope as well as normal saline irrigation fluid (0.9% NaCl) for endoscopic vision.

4.3 NUMBER OF INVESTIGATIONAL DEVICES TO BE USED

Each patient will only receive one novel ureteric stent, resulting in a total of 50 required investigational devices. However, additional investigational devices are to be made available (as per Table 3) in case of any issues with the device or packaging*, and to allow for clinicians to select the most appropriate sized stent for each patient.* Depending on the need, extra quantities will be manufactured.

Table 3 - Stent quantities based on variation of size

Length (cm) / Size (French)	22cm	24cm	26cm	28cm	
6	10	20	20	50	100
8	10	20	20	20	70
				SUM	170

4.4 TRAINING AND EXPERIENCE

The novel ureteric stent is designed for insertion by urological surgeons. These surgeons will already have comprehensive clinical training and experience covering the indications for ureteric stent (also known as ureteral) drainage, and for performing the procedure itself. Accordingly, they will have appropriate expertise for stent insertion, the post operative management of patients with a stent *in situ* and for the subsequent removal or replacement of stents. Instructions for use of the novel stent are the same as conventional stents and are provided within the novel stent package.

The patient receiving the novel stent does not require any training and does not have any need to "interact" with the device whilst it is indwelling, but for this clinical investigation, all participants must have had a stent in the past (according to the inclusion criteria). As part of their standard care, all patients receiving any stent insertion will be advised about potential side effects attributable to ureteric stents, including strategies to mitigate these. In particular, they will be informed about the stent symptoms to be expected (as detailed in section 7.4) including cystitis-like symptoms such as frequency/urgency of urination and bladder spasm, pain from/to the loin, and the potential for visible blood in the urine. Patients will be advised that the stend dwell time should be less than 6 months to reduce encrustation and side effects. All potential side effects are additionally detailed in the Patient Information Sheet that all participants will receive.

4.5 MEDICAL OR SURGICAL PROCEDURES

The surgical procedure required to insert the novel ureteric stent is the same as the technique required for the insertion of other ureteric stents currently on the market. The process is summarised below:

- A guide wire is passed through a cystoscope to the kidney under endoscopic and fluoroscopic control. It is recommended doing a retrograde pyelogram before proceeding to stent insertion to delineate the anatomy of the upper urinary tract. A ureteric catheter is therefore advanced over the guidewire, which is then removed, to perform a retrograde pyelogram with contrast through the lumen of the ureteric catheter.

- The guidewire is then replaced via the ureteric catheter lumen, before removing the ureteric catheter leaving the guidewire in an appropriate position in the kidney collecting system. The stent is placed over the distal end of the wire, with the tapered end leading, and using screening fluoroscopy is advanced into the ureter initially followed by the pusher over the supported guide wire. Note: The size of the stent will be judged using details of previous stent insertion, or based on standard clinical judgements for this such as the patient's height, ureteric length on pre-operative CT imaging, and the length of ureteric catheter required to reach the kidney for the retrograde study.

- The stent is advanced up the ureter into the kidney using the pusher until the proximal end of the stent is visible overlying the pyelogram of the kidney on fluoroscopy. Note: the location and orientation of the stent and the amount of the coil/loop is decided with clinical judgement. It is recommended to visualise the proximal end of the sent using fluoroscopy and distal end under vision with the cystoscope. A visible graduation mark on the distal aspect of the stent just proximal to the bladder coil will allow the operator to know how much of the stent remains before it is deployed at the ureteric orifice.

- Once this has been achieved, and the stent is adequately positioned within the renal pelvis and the bladder, the wire is removed from the stent lumen which will spontaneously coil proximally in the renal collecting system and distally in bladder instantly.

The subsequent removal of the novel ureteric stent is performed in the same way as currently marketed ureteric stents.

4.6 DEVICE ACOUNTABILITY

Device accountability is detailed in Cassette Medical Device Accountability Document which will be stored in the Cassette Trial Management Folder.

5 SELECTION AND ENROLMENT OF PARTICIPANTS

5.1 PARTICIPANT ENROLMENT

The total expected duration of the clinical investigation will be 16 months. 25 Oncology and 25 Kidney stone patients will be recruited across both sites from UCLH and UHS. Kidney stone patients will be in the study for approximately 4 weeks plus follow-up period, and the Oncology patients will be in the study for approximately 25 weeks plus follow-up period. The recruitment period is 12 months. The inclusion criteria are outlined below. Pregnancy prior to stent insertion is an exclusion criterion, however, any participant that becomes pregnant throughout the duration of the study, will remain in the trial (if they wish) - they will be monitored for any safety related issues and will be followed up until the end of their pregnancy. Only consented patients who are eligible and enrolled into the study will be considered trial participants. Those who do not have the novel ureteric stent inserted will be replaced.

5.2 CONSENT

The Principal Investigator (PI) retains overall responsibility for the conduct of the research at their site, including receiving informed consent from participants. They must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained, and competent to participate.

Consent to enter the trial must be sought from each participant only after a full explanation has been given, a Participant Information Sheet (PIS) offered, and time allowed for consideration. Informed consent must be obtained prior to the participant undergoing procedures that are specifically for the purpose of the trial.
The right of the participant to refuse to participate without giving reasons must be respected.
Should the patient participate in the trial, the site trial team will provide a letter informing the patient's GP of the trial and the patient's involvement. If the participant changes GP practice, then the site trial team should inform the patients new healthcare professional.

After the participant has entered the trial, their healthcare team remains free to give alternative treatment to that specified in the CIP at any stage if they feel it is in the participant's best interest. The reasons for doing so should be recorded in the patients' medical notes.

All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment. Participants must be provided with a contact point where they may obtain further information about the trial.

Participants will be provided with a patient information sheet (either in-person at an early pre-surgery consultation [up to 8 weeks prior to surgery], or online, or via post). Where possible, patients will ideally be provided this information sheet at least 24 hours prior to making a decision to provide their consent. Consent will be obtained in person with a member of the site team present, at a pre-surgery consultation (within a few days prior to surgery), or on the day of surgery.

Upon completion of the informed consent form, a copy will be given to the participant, a copy stored in the participant's medical notes, the original filed in the site trial file and a copy of the consent form will be sent to the SCTU using the University of Southampton's SafeSend service (https://safesend.soton.ac.uk/), to allow for central monitoring. SafeSend is the safest and most secure (data protection compliant) mechanism for the sites to send relevant the informed consent forms to SCTU as it is hosted by the University of Southampton and supports both in-transit and at-rest encryption.

5.3 INCLUSION CRITERIA

1. Aged 18 years or over
2. Ureteric stents clinically indicated either due to kidney stones or abdominal/pelvic cancers compressing ureters
3. Previous lived experience with ureteric stents
4. Awaiting insersion/replacement of stents
5. Ability to give consent
6. Ability to interact with online and written study documentation
7. Sufficient English to complete study documentation and questionnaires

5.4 EXCLUSION CRITERIA

8. Expected survival <4months
9. Unfit for stent insertion
10. Unable to comply with study processes

11. Pregnancy occuring prior to stent insertion
12. Planned stent removal is not at the same hospital as the stent insertion

6 TRIAL PROCEDURES

6.1 RECRUITMENT

6.1.1 Participant Identification

Potentially eligible patients will be identified by the clinical teams at site by screening surgery lists for ureteric stent removal/replacement/insertion. Patients listed for surgery to insert/replace their ureteric stent will be sent an invitation letter explaining the study in brief and a Patient Information Sheet for the study or given one at the first pre-surgery consultation.

6.2 SCREENING PROCEDURES

Screening procedures will include identifying and sending out Patient Information Sheets to potentially eligible patients and a medical history review (to narrow down potentially eligible patients), as well as standard of care physical examinations and laboratory tests (pre-op anaesthetic tests – as required by the clinicial team). Participants should be recruited within 8 weeks of screening.

6.2.1 Screen Failures

Screen failures are defined as patients with whom the CASSETTE trial is discussed but who do not go on to be enrolled in the trial. This will include patients who consented but were not eligible for inclusion. Screen failures will be documented in screening logs, together with reasons for exclusion. Site screening logs will be filed in the ISF and emailed monthly to cassette@soton.ac.uk.

6.2.2 Payment

Please see section 11.4

6.3 REGISTRATION AND RANDOMISATION PROCEDURES

6.3.1 Registration

At each site, participants who meet the eligibility criteria for the study and for whom written informed consent has been obtained will be added to the database which will generate a study ID for the participant. This will only be accessible by delegated site staff. A notification from the database will be sent to cassette@soton.ac.uk to centrally document study registrations.

6.4 TRIAL PROCEDURES – ALL PATIENTS

6.4.1 Screening Day 0 (up to 8 weeks prior to day of surgery)

The clinical team at site will discuss the upcoming surgery with the patient as well as their potential participation in the study. This consultation can take place face-to-face or remotely (video or telephone call). Patients will have the opportunity to discuss their potential participation in the study and any questions with the clinical team.

If a patient does not wish to take part in the trial but is interested in sharing their experiences of ureteric stents, and reasons for not wishing to take part in the trial, the clinical team can take consent for sharing the patient's contact details (telephone, email address, postal address) with the qualitative interviewer at the University of Southampton.

The clinical team will share contact details of patients who agreed to be contacted regarding the qualitative interview with the qualitative researcher, see section 6.7.3.

6.5 TRIAL PROCEDURES – KIDNEY STONE PATIENTS

6.5.1 Day of Surgery 1

- The clinical team will take informed consent (if not already received)
- Assessment of patient eligibility (including standard of care pregnancy test – required to confirm eligibility)
- Patient history assessment
- Physical Exam
- Check for Adverse Events/Device Deficiencies
- Register patient onto the database
- Prior to novel ureteric stent insertion, patients will be asked to complete *CASSETTE (Kidney Stone) Patient Questionnaire – BASELINE** questionnaire on paper

**Kidney stone baseline (no current stent in place) questionnaires includes:*

- *EQ5D-5L*
- *Subject demographics*
- *Short Version Stent Quality of Life (no current stent in place)*
- *USI-QoL – Stone disease*

**Kidney stone baseline (current stent in place) questionnaire includes:*

- *EQ5D-5L*
- *Ureteric Stent Symptoms Questionnaire (with a stent in place) [USSQ]*
- *Subject demographics*
- *Short Version Stent Quality of Life (stent in place)*
- *USI-QoL – Stone disease*

The clinician will then perform surgery (for the purpose of this study this is called surgery 1) and inserts the novel ureteric stent (this may be a replacement of pre-existing stent). Any adverse events occurring during the surgery (either as a result of the removal of the old stent, or the insertion of the novel stent), as well as any device deficiencies occurring with the novel stent, must be recorded on the database.

6.5.2 4-7 days post-Surgery 1

Patients will be asked to complete *CASSETTE (Kidney Stone) Patient In Situ Questionnaire – 4-7 days after Surgery 1** questionnaire online, or if completed on paper, the questionnaires will be returned to the site team using a freepost envelope. (Sites can also collect questionnaires over the phone with the participant if the participant choses this option)

**Kidney stone in situ (4-7 days after surgery 1) questionnaire includes:*

- *EQ5D-5L*
- *Antibiotics/Hospitalisation*
- *Short Version Stent Quality of Life*
- *USI-QoL – Stone disease*
- *Ureteric Stent Symptoms Questionnaire (with a stent in place) [USSQ]*

6.5.3 Within 24hrs prior to Surgery 2

Patients will be asked to complete *CASSETTE (Kidney Stone) Patient In Situ Questionnaire - Surgery 2** questionnaire online, or if completed on paper, the participants should bring the questionnaires with them to the day of removal surgery**.** (Sites can also collect questionnaires over the phone with the participant if the participant choses this option)

**Kidney stone in situ (Surgery 2) questionnaire includes:*

- *EQ5D-5L*
- *Antibiotics/Hospitalisation*
- *Short Version Stent Quality of Life*

- *USI-QoL – Stone disease*
- *Ureteric Stent Symptoms Questionnaire (with a stent in place) [USSQ]*

6.5.4 Day of Surgery 2

The clinical team performs surgery 2 and removes the experimental (novel) ureteric stent (and replaces with standard of care ureteric stent as applicable). For kidney stone patients, this will take place approximately 4 weeks after insertion. The novel ureteric stents can be removed earlier if deemed necessary by the treating clinician. At this stage, the clinical team will collect information relating to any adverse events and device deficiencies and record these on the database.

The clinical team will collect a urine sample and the experimental (novel) ureteric stent following the procedures detailed in the laboratory manual. The clinical team will perform any standard of care procedures as required, including performing safety blood tests. These will be detailed in the patients' medical notes and will only be collected as part of the trial data if clinically relevant.

6.5.5 Two to three (2-3) weeks post-Surgery 2

Patients will be asked to complete *CASSETTE (Kidney Stone) Patient Questionnaire – Post Removal surgery** questionnaire online or if completed on paper, the questionnaires will be returned to the site team using a freepost envelope.

**Kidney stone (post-removal surgery) questionnaire includes:*

- *EQ5D-5L*
- *Antibiotics/Hospitalisation*
- *Short Version Stent Quality of Life*
- *USI-QoL – Stone disease*
- *Ureteric Stent Symptoms Questionnaire (after stent removed) [USSQ]*
-

The site research team will also contact the patient by telephone to collect any AEs/DDs as appropriate 1-3 weeks post-surgery 2. If the phone call is to happen at week 2 or 3, then sites can also collect the questionnaires over the phone with the participant if the participant choses this option.

6.6 TRIAL PROCEDURES – ONCOLOGY PATIENTS

6.6.1 Day of Surgery 1

- The clinical team will take informed consent (if not already received)
- Assessment of patient eligibility (including standard of care pregnancy test – required to confirm eligibility)
- Patient history assessment
- Physical Exam
- Check for Adverse Events/Device Deficiencies
- Register patient onto the database
- Prior to novel ureteric stent insertion, patients will be asked to complete *CASSETTE (Oncology) Patient Questionnaire – BASELINE** questionnaire on paper

**Oncology baseline (no current stent in place) questionnaires includes:*

- *Subject demographics*
- *Short Version Stent Quality of Life (no current stent in place)*
- *EQ-5D-5L*

**Oncology baseline (current stent in place) questionnaire includes:*

- *Subject demographics*
- *Short Version Stent Quality of Life (stent in place)*
- *EQ-5D-5L*
- *Ureteric Stent Symptoms Questionnaire (in-situ) [USSQ]*

The clinician will then perform surgery (for the purpose of this study this is called surgery 1) and inserts the novel ureteric stent (this may be a replacement of pre-existing stent). Any adverse events occurring during the surgery (either as a result of the removal of the old stent, or the insertion of the novel stent), as well as any device deficiencies occurring with the novel stent, must be recorded on the database.

6.6.2 4-7 days post-Surgery 1

Patients will be asked to complete *CASSETTE (Oncology) Patient In Situ Questionnaire – 4-7 days after Surgery 1** questionnaire online, or if completed on paper, the questionnaires will be returned to the site team using a freepost envelope. (Sites can also collect questionnaires over the phone with the participant if the participant choses this option)

**Oncology in situ (4-7 days after surgery) questionnaire includes:*

- *Antibiotics/Hospitalisation*
- *Short Version Stent Quality of Life*
- *EQ-5D-5L*
- *Ureteric Stent Symptoms Questionnaire (with a stent in place) [USSQ]*

6.6.3 Halfway between Surgery 1 and Surgery 2 (mid-point to be based on planned removal/replacement date +/- 1 week)

Patients will be asked to complete *CASSETTE (Oncology) Patient In-Situ Questionnaire - Halfway** questionnaire online, or if completed on paper, the questionnaires will be returned to the site team using a freepost envelope.

**Oncology in situ (Halfway) questionnaire includes:*

- *Antibiotics/Hospitalisation*
- *Short Version Stent Quality of Life*
- *EQ-5D-5L*
- *Ureteric Stent Symptoms Questionnaire (with a stent in place) [USSQ]*

The site research team will also contact the patient by telephone to collect any AEs/DDs as appropriate. Sites can also collect the questionnaires over the phone with the participant at this time point, if the participant choses this option.

6.6.4 Within 24hrs prior to Surgery 2

Patients will be asked to complete *CASSETTE (Oncology) Patient In-Situ Questionnaire - Surgery 2** questionnaire online, or if completed on paper, the participants should bring the questionnaires with them to the day of removal surgery**.** (Sites can also collect questionnaires over the phone with the participant if the participant choses this option)

**Oncology in situ (Surgery 2) questionnaire includes:*

- *Antibiotics/Hospitalisation*
- *Short Version Stent Quality of Life*
- *EQ-5D-5L*
- *Ureteric Stent Symptoms Questionnaire (with a stent in place) [USSQ]*

6.6.5 Day of Surgery 2

The clinical team performs surgery and removes the novel ureteric stent (a standard of care ureteric stent may be replaced during this surgery as required). For oncology patients, this will take place approximately 25 weeks after insertion. The novel ureteric stents can be removed earlier if deemed necessary by the treating clinician. The novel ureteric stents can be removed earlier if deemed necessary by the treating clinician. At this stage, the clinical team will collect information relating to any adverse events and device deficiencies and record these on the database.

The clinical team will collect a urine sample and the experimental (novel) ureteric stent following the

procedures detailed in the laboratory manual. These will be analysed. The clinical team will perform any standard of care procedures as required, including performing safety blood tests. These will be detailed in the patients' medical notes and will only be collected as part of the trial data if clinically relevant.

6.6.6 Two to three (2-3) weeks post-Surgery 2

Patients will be asked to complete *CASSETTE (Oncology) Patient Questionnaire – Post Surgery 2** questionnaire online or if completed on paper, the questionnaires will be returned to the site team using a freepost envelope.

**Oncology (post-Surgery 2) questionnaire includes:*

- *Antibiotics/Hospitalisation*
- *Short Version Stent Quality of Life*
- *EQ-5D-5L*
- *Ureteric Stent Symptoms Questionnaire (after stent removal) [USSQ]*

The site research team will also contact the patient by telephone to collect any AEs/DDs as appropriate 1-3 weeks post-surgery 2. If the phone call is to happen at week 2 or 3, then sites can also collect the questionnaires over the phone with the participant if the participant choses this option.

6.7 TRIAL PROCEDURES – QUALITATIVE INTERVIEWS

6.7.1 Qualitative interviews – Clinician cohort

At least ten (until sample saturation), clinicians (Consultants (if doctors) or equivalent to senior staff nurse (band 6) and above) who have experience of managing patients with ureteric stents and have been involved in managing patients in this trial with the novel ureteric stents, or those who may be interested in using the novel ureteric stent will initially be contacted by the CASSETTE Principal Investigators from each site to make them aware of the chance to participate in a qualitative interview and each clinician will be invited to email the CASSETTE study team to express their interest in participating. The CASSETTE study team will then share their details with the qualitative researcher at the University of Southampton. The qualitative researcher will invite clinicians to an interview (up to 45 minutes by telephone or video call). All clinicians will be given a copy of the clinician participant information sheet about these interviews. They will also be sent an email, a text and/or an invitation letter prior to their qualitative interview to remind them of their appointment if they wish to take part. The interviews with the clinicians will take place towards the last 3 months of the trial.

6.7.2 Qualitative interviews – Patient cohort

Patients will have the option to consent to being contacted about taking part in the qualitative interviews, at the same time as consenting to the main trial. If they do not wish to take part in the main trial, they will still have the option to provide consent for their details to be shared with the qualitative researcher. The qualitative researcher (at the University of Southampton) will contact the patients who consented to their contact details being shared and discuss any potential questions and to arrange a time to speak with them by telephone or video call. They will also be sent an email, a text, and/or an invitation letter prior to their qualitative interview to remind them of their appointment. The interviews with participants will take place after their stent has been removed and the completion of the follow-up questionnaire.

6.7.3 Qualitative interviews – Consent

During the telephone or video call, the qualitative researcher will check if the patient/clinician has read the Patient/Clinician Information Sheet, whether they understood it and whether they have any questions. They will then proceed to take verbal consent for participation in the qualitative interview study over the telephone or video call. The researcher will read out the consent questions included in the Interview Guide over the telephone or video call so that the patient/clinician can give verbal consent if they wish the interview to proceed. The verbal consent will be digitally recorded and stored securely. Patients/clinicians

will be given a free choice and will be free to withdraw consent at any time. If the patient does not give consent for recording of consent and the subsequent interview, consent will not be collected, and this will be recorded as a screen failure for the qualitative sub-study.

6.7.4 Qualitative interview conduct

The interviews with all participants will take place via telephone or video call, but the recording of the interviews will be online using a web-conference recorder (e.g. MS Teams) or on a physical recorder. The interviews, which will be up to 45 minutes in duration, will be semi-structured following an interview guide (see interview guide); this will enable topics crucial to the research to be covered whilst also providing the flexibility for participants to introduce pertinent issues.

The patients will be asked about their experiences of having a ureteric stent and complications which they experienced. If patients mention any issues that have not previously been recorded as adverse events or device deficiencies, these will be recorded in the database as per section 7 of this CIP.
Clinicians will be asked about their experiences of managing patients with ureteric stents. If the clinician mentions any issues with the device or instructions or surgery, these will have to be collected as adverse events or device deficiencies (please refer to section 7.2.2 of the CIP).

If the patient or the clinical interviewee mentions any information which the interview suspects to be related to adverse events or device deficiencies during the interview, the medically qualified interviewer will review the transcript from the interview and they will also provide the relevant site PI with the transcript from the interview for the clinician to confirm the adverse event or the device deficiency. If confirmed, the relevant site PI will need to check the database to see if the mentioned events have been recorded. If the relevant site PI confirms the adverse event or device deficiency which previously has not been recorded, then the interviewer will ask the patient or the clinical interviewee for the start and end date and the outcome of the event was. The interviewer will then need to send this information, via email to the relevant site staff, copying the CASSETTE trial inbox into the correspondence so that the CASSETTE trial team can follow this up.

Participants (both clinicians and patients) in the interview will receive a voucher worth £10 to thank them for their time.

The consent forms and audio-recordings will be stored until the end of the CASSETTE study and then destroyed as per UKDS recommendations (https://www.ukdataservice.ac.uk/manage-data/store/disposal). Although the digital recordings are not encrypted, measure will be taken to ensure the information remains secure. The qualitative researcher will keep the device in a locked drawer or secure place when not in use. Only the researcher or study team will have access to the locked drawer or cupboard. The recording will be uploaded at the first opportunity, and then the recording will be deleted from the device. Trial ID's will be assigned to those who consented to the main part and the qualitative sub study. For those participants who are only taking part in the qualitative sub study, a screening ID should be used. A participant identifier code is applied to each audio file captured. A member of staff will also obtain written consent for your contact details to be passed onto the qualitative researcher and the consent forms will be submitted to the CASSETTE study team via SafeSend. All data including personal identifiable information will be stored in a secure folder on the University of Southampton server and will only be accessible to members of the research team from University of Southampton.

6.8 TRIAL INTERVENTION DISCONTINUATION AND PARTICIPANT WITHDRAWAL

Participants may withdraw voluntarily from the trial, or the Principal Investigator/Treating Healthcare Provider may discontinue a participant from the trial treatment for appropriate medical reasons.

6.8.1 Discontinuation of Trial Intervention

a) Early stent removal

- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the trial would not be in the best interest of the participant
- Disease progression or other clinical situation such that continued participation in the trial would not be in the best interest of the participant

b) Discontinuation of trial intervention, but not suitable for removal

- If the participant develops an exclusion criterion that makes the change/removal of their stent unnecessary or inappropriate (either newly developed or not previously recognized) that precludes further trial participation
    a. Expected survival <4 months
    b. Unfit for stent removal/change
    c. Unable to comply with study processes
- Participant unable to receive trial intervention within a defined time period by clinicians on case-by-case basis.

While pregnancy prior to stent insertion is an exclusion criteria, if a participant becomes pregnant after stent insertion, they will be followed up by the relevant clinician and remain in the trial.

The data to be collected at the time of trial intervention discontinuation will include the reason for discontinuation. Early removal which is due to the participant no longer needing the stent will be deemed as a success factor for the study. Where early removal is due to complications/symptoms, then clinical data will be collected on an eCRF in the trial database. In all cases, full details of the reason for trial intervention discontinuation should be recorded in the eCRF and participant's medical record.

6.8.2 Trial Withdrawal

The participant is free to withdraw consent from the trial at any time, without providing a reason, and without their medical care or legal rights being adversely affected. If a patient withdraws before having their stent inserted, or if a stent is not inserted due to a clinical decision, then they will be replaced. Similarly, if a patient's stent is removed at any other hospital other than UCLH, or UHS then the participant will also be replaced.

Investigators should explain to participants the value of remaining in trial follow-up and allowing this data to be used for trial purposes. Where possible, participants who have withdrawn from the trial intervention should continue with relevant trial-associated processes as per the Schedule of Observations and Procedures. If participants additionally withdraw consent for this, they should revert to standard clinical care/follow-up as deemed by the responsible clinician. It would remain useful for the trial team to continue to collect any routine data (i.e., data that can be collected with no impact on the participant beyond standard clinical care/follow-up), and this will continue unless the participant explicitly requests otherwise. If this is requested, this constitutes complete withdrawal from the trial and should be recorded as end of study for the participant in the relevant eCRF and in their medical record, and no further data should be collected for this participant.

Patients who withdraw (or are withdrawn from the trial) may continue to consent and participate in the qualitative interviews if they wish, regardless of their level of withdrawal or the duration of their trial participation.

6.9 STORAGE AND ANALYSIS OF CLINICAL SAMPLES

Procedures for dealing with urine samples and removed ureteric stents (collection, transport, analysis, storage, and destruction) are detailed in the Laboratory Manual. Samples will be destroyed following analysis, as per local standard procedures.

6.10 DEFINITION OF END OF TRIAL

The end of trial is defined as the date when database has been frozen following the resolution of data queries, as far as possible, as agreed by the Trial Management Group.

7 SAFETY

7.1 DEFINITIONS

Standard BS EN ISO 14155:2020 (in combination with the UK Medical Device Regulations 2002, as amended) provides the following definitions relating to adverse events in medical device trials:

Device deficiency	Inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions[1], use error[2], or inadequacy in the information supplied by the manufacturer. *Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling. These include deficiencies related to both the investigational medical device, or the comparator*
Serious health threat	Signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health of subjects, users, or other persons, and that requires prompt remedial action for other subjects, users, or other persons *This would include events that are of significant and unexpected nature, such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals*
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational medical device (and whether anticipated or unanticipated). *This includes events related to the investigational medical device or comparator. For subjects, this includes events related to all procedures involved. For users or other persons, this is restricted to events related to the use of investigational medical devices or comparators.*
Serious Adverse Event (SAE)	Any adverse event which: • Results in death • Is life threatening • Requires hospitalisation or prolongation of existing hospitalisation • Results in persistent or significant disability or incapacity; or • Requires medical or surgical intervention to prevent a life-threatening illness or injury, or persistent or significant disability or incapacity • Foetal distress, foetal death, a congenital abnormality, or birth defect including physical or mental impairment*; or* • *Is otherwise considered medically significant by the investigator*

	Planned hospitalisation for a pre-existing condition, or a procedure required by the Clinical Investigation Plan (Study Protocol) without serious deterioration in health, is not considered a serious adverse event
Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device. *This includes any adverse event resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation; or any malfunction of the investigational medical device. This includes any event resulting from use error or from intentional misuse of the investigational medical device. This includes the comparator, where the comparator is also a medical device.*
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Anticipated Serious Adverse Device Effect (ASADE)	Serious adverse device effect (SADE) which by its nature, incidence, severity, or outcome has been identified in the current risk assessment.
Unanticipated Serious Adverse Device Effect (USADE)	Serious adverse device effect (SADE) which by its nature, incidence, severity, or outcome has **not** been identified in the current risk assessment.

1. *failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the IFU, CIP, or IB*
2. *user action or lack of user action while using the medical device that leads to a different result than that intended by the manufacturer or expected by the user:*
    a. *includes the inability of the user to complete a task*
    b. *users may or may not be aware that a use error has occurred*

7.2 TRIAL SPECIFIC REQUIREMENTS

7.2.1 Adverse Events

All Adverse Events (AEs) that are related to the experimental stent, or that relate to the medical condition requiring the stent should be reported on the Adverse Event eCRF. Reporting period starts from date of day of insertion of novel ureteric stent (Surgery 1) up until the date of the return of the last questionnaire, the date of the follow up phone call, or the date of the qualitative interview for patients that consent to the qualitative sub-study, whichever is the later.

7.2.2 Device Deficiencies

Device deficiencies occurring between receipt at site and prior to their selection for insertion in a participant, should follow the procedures detailed in the CASSETTE Device Accountability document. Device deficiencies occurring after the device is selected for insertion in a participant (whether inserted or not) will be collected on the device deficiency (e)CRF for that specific participant.

Additionally, trial clinicians will assess whether or not these *<u>might</u>* have led to an SAE if:

i. suitable actions had not been taken, or
ii. intervention had not been made, or

iii. if circumstances had been less fortunate

If the device deficiency fulfils the reportable criteria above, then the event will also be reported to SCTU using the Serious Adverse Event Report Form for assessment and onward reporting as appropriate.

7.2.3 Seriousness

A complete assessment of the seriousness must always be assessed by a medically qualified doctor who is registered on the delegation of responsibility log; this is usually the investigator.

All reportable adverse events that fulfil the criteria definition of 'serious' in CIP section 7.1, must be reported to SCTU using the Serious Adverse Event Report Form. Specific exceptions to this (as listed below) should be recorded as AEs rather than SAEs.

7.2.4 Exceptions:

For the purposes of this trial, the following **SAEs do not** require reporting to SCTU using the Serious Adverse Event Report Form:

- Hospitalisations for elective treatment of a pre-existing condition (the pre-existing condition needs to have been captured within the medical history CRF and/or the patient's medical notes).

7.3 CAUSALITY

A complete assessment of the causality must always be made by a medically qualified doctor who is registered on the delegation of responsibility log; this is usually the investigator.

If any doubt about the causality exists, the local investigator should inform SCTU who will notify the Chief Investigator. Other clinicians may be asked for advice in these cases.

In the case of discrepant views on causality, SCTU will classify the event as per the worst case classification and if onward reporting is required, the MHRA and/or REC will be informed of both parties' points of view.

Relationship	Description	Denoted
Not related	Relationship to the device or procedures can be excluded when: • The event is not a known side effect of the product category the device belongs to, or of similar devices and procedures • The event has no temporal relationship with the use of the investigational device or the procedures • The event does not follow a known response pattern to the medical device, and is biologically implausible • The discontinuation of medical device application (or the reduction of the level of activation/exposure [when clinically feasible]) and reintroduction of its use (or increase the level of activation/exposure), do not impact on the serious event • The event involves a body-site or an organ not expected to be affected by the device or procedure • The serious event can be attributed to another cause (e.g. an underlying or concurrent illness/clinical condition, an effect of another device, drug, treatment or other risk factors)	SAE

	• The event does not depend on a false result given by the investigational device used for diagnosis, when applicable • Harms to the subject are not clearly due to use error *In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.*	
Unlikely	The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained	SAE
Possible	The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/clinical condition or/and an effect of another device, drug or treatment). *Cases where relatedness cannot be assessed or no information has been obtained should also be classified as possible.*	Anticipated or Unanticipated Serious Adverse Device Effect (ASADE or USADE)
Probable	The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably be explained by another cause, but additional information may be obtained.	Anticipated or Unanticipated Serious Adverse Device Effect (ASADE or USADE)

Causal relationship	The serious event is associated with the investigational device or with procedures beyond reasonable doubt when:
	• The event is a known side effect of the product category the device belongs to or of similar devices and procedures
	• The event has a temporal relationship with investigational device use/application or procedures
	• The event involves a body-site or organ that
	  o The investigational device or procedures are applied to;
	  o The investigational device of procedures have an effect on
	• The serious event follows a known response pattern to the medical device (if the response pattern is previously known)
	• The discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure) impacts on the serious event (when clinically feasible)
	• Other possible causes (e.g. an underlying or concurrent illness/clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out
	• Harm to the subject is due to error in use
	• The event depends on a false result given by the investigational device used for diagnosis (when applicable)
	In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.
		Anticipated or Unanticipated Serious Adverse Device Effect (ASADE or USADE)

7.4 EXPECTEDNESS

Expectedness assessments are made against the list of expected events as detailed in the IB and referred to in sections 7.4.1 and 7.4.2 below. The nature and/or severity of the event should be considered when making the assessment of expectedness. If these factors are not consistent with the current information available, then the AE or device deficiency should be recorded as 'unexpected'.

7.4.1 Device Deficiencies

- Insertion (difficulty to advance because of stent buckling on the side hole)
- Removal (stent fracturing on side holes)
- Encrustation and biofilm formation (E&B) leading to failure to drain
- Functional challenges (failing to drain)

7.4.2 Adverse Events

- Cystitis (and associated symptoms)
- Urinary tract infection (and associated symptoms)
- Haematuria
- Loin pain
- Encrustation and biofilm formation

7.5 REPORTING PROCEDURES

Any questions concerning adverse event reporting should be directed to the SCTU in the first instance. A flowchart will be provided to aid in the reporting procedures.

7.5.1 Reporting Details

7.5.1.1 Adverse Events

All AEs that are related to the experimental stent, or that relate to the medical condition requiring the stent should be recorded on the eCRF as per the trial specific requirements listed in Section 7.2.1.

7.5.1.2 Device Deficiencies

All device deficiencies should be sent to the CASSETTE SCTU Trial Team via email (**only those not relating to a participant**) or recorded on the Device Deficiency eCRF as per the trial specific requirements listed in section 7.2.2.

7.5.1.3 Serious Adverse Events

For all reportable SAEs and device deficiencies, an SAE report form should be completed with as much detail as possible (including any relevant anonymised treatment forms and/or investigation reports) and emailed to SCTU immediately but at least within 3 days of site becoming aware of the event.

Or
Contact SCTU by phone for advice and then email a scanned copy of the SAE report form completed as above.

SAE REPORTING CONTACT DETAILS

Please email a copy of the SAE form to
SCTU within 3 days of becoming aware of the event

Email: ctu@soton.ac.uk

FAO: Quality and Regulatory Team

For further assistance: Tel: 023 8120 5154 (Mon to Fri 09:00 – 17:00)

The event term should be the most appropriate medical term or concept (for adverse events) or technical term or concept (for device deficiencies) in the opinion of the assessing investigator.

Additional information should be provided as soon as possible if all information was not included at the time of reporting.

As per regulatory and local SCTU procedures, all SAEs and device deficiencies that might have led to an SAE as detailed in section 7.2.2 will be reported to the MHRA. Additionally, SAEs will be reported to the REC, if the event was:

- 'Related' – i.e., resulted from the administration of any of the research procedures; and
- 'Unexpected' – i.e., an event that is not listed in the CIP as an expected occurrence.

7.5.1.4 Reporting Timelines

All CIP reportable AEs and SAEs should be reported from date of day of insertion of novel ureteric stent up until the date of the return of the last questionnaire, the date of the follow up phone call, or the date of the qualitative interview for patients that consent to the qualitative sub-study, whichever is the later.

All unresolved adverse events should be followed up by the investigator until one of the end of trial criteria is met (i.e. lost to follow up, withdrawal etc.). Upon receiving the last completed post-surgery questionnaire from the participant, or upon completion of the qualitative interview, the investigator should instruct each participant to report any subsequent event(s) that the participant believes might reasonably be related to participation in this trial. The investigator should notify the trial sponsor of any death or adverse event occurring at any time after a participant has discontinued or terminated trial participation that may reasonably be related to this trial.

7.5.2 Pre-existing Conditions

- Pre-existing conditions (prior to informed consent) should not be reported as an AE unless the conditions worsen during the trial. Instead, they will need to be recorded on the Medical History eCRF, within the trial database.

7.5.3 Pregnancy

Pregnancy is not considered an AE unless a negative or consequential outcome is recorded for the mother or child/foetus. If the outcome meets the serious criteria, this would be considered an SAE and should be reported as detailed in section 7.5.1.

1) Pregnancy prior to stent insertion is an exclusion criterion and must result inpatient withdrawal. These pregnancies do not need to be followed up, but 'pregnancy' should be captured on the EoS form.
2) Participants who become pregnant after stent removal (Surgery 2) will not need to be withdrawn, nor will their pregnancies need to be followed up. The dates of the pregnancy will be required to be recorded to ensure that follow-up is not needed. This will need to be documented on the pregnancy notification form.
3) Pregnancies that occur in participants whilst a novel stent is in situ will require a pregnancy notification form to be completed on the eCRF. These pregnancies should be followed up by site until at least birth (if consent from participant is obtained for this).

7.6 RESPONSIBILITIES

7.6.1 Principal Investigator (PI)

The PI, or medically qualified doctor who is registered on the delegation of responsibility log, is responsible for:

1. Using medical judgement in assigning seriousness, causality and if requested, whether the event was anticipated using the expectedness information approved for the trial (as detailed in Section 7.4)
2. Ensuring that all reportable SAEs and device deficiencies are recorded and reported to the SCTU immediately, or at least within 24 hours, of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that reportable events are chased with the SCTU if a record of receipt is not received within 1 working day of initial reporting.
3. Ensuring that AEs are recorded and reported to the SCTU in line with the requirements of the CIP.
4. Delegated Chief Investigator responsibilities detailed in section 7.6.2 below.

7.6.2 Chief Investigator (CI) / delegate or independent clinical reviewer:

The Chief Investigator (CI) is responsible for ***delegating*** the following responsibilities to each Principal Investigator at their relevant site for:

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk/ benefit.
2. Upon request review coding decisions

7.6.3 Independent clinical reviewer

The delegated clinical reviewer is responsible for the below tasks. The Principal Investigator for each site will have the responsibility of clinically reviewing and providing a second opinion on all SAE's that occur at each other's site.

1. Using medical judgement in assigning the SAEs seriousness, causality and whether, if requested, the event was anticipated (in line with the expectedness information) where it is required as a second clinical opinion or if it has not been possible to obtain local medical assessment.
2. Immediate review of all USADEs
3. Review of specific SAEs and related SAEs in accordance with the trial risk assessment and CIP as detailed in the Trial Monitoring Plan.

7.6.4 Sponsor / delegate

The Sponsor, or delegate, is responsible for:

1. Central data collection and verification of device deficiencies, AEs and SAEs, according to the CIP onto a database/paper forms.
2. Reporting safety information to the independent clinical reviewer(s) for the ongoing assessment of the risk / benefit according to the Trial Monitoring Plan.
3. Checking causally related events against the approved expectedness information, in place at time of event onset.
4. Reporting safety information to the Data Monitoring & Ethics Committee (DMEC) according to the Trial Monitoring Plan.
5. Ensuring the expedited reporting of all reportable SAEs and device deficiencies to the Competent Authority (MHRA in UK) within required timelines
6. Ensuring expedited reporting of related and unexpected serious adverse events to the REC within the required timelines.
7. Notifying Investigators of related and unexpected serious adverse events that occur within the trial.
8. Quarterly reporting of summary SAE data to the Competent Authority (MHRA in UK)
9. Notifying PIs of updates to the Reference Safety Information for the trial.

7.7 REPORTING URGENT SAFETY MEASURES

If any urgent safety measures are taken the CI/Sponsor shall immediately, and in any event no later than 3 days from the date the measures are taken, give written notice to the MHRA and REC of the measures taken and the circumstances giving rise to those measures.

8 STATISTICS AND DATA ANALYSES

8.1 ANALYSIS POPULATIONS

Intention-to-treat (ITT) population: All patients entered in the trial.
Safety population: All patients who attempted to insert the stent.
As-treated population: All patients who completed Surgery 1.
Per-protocol population: All patients who completed Surgeries 1 and 2

8.2 METHOD OF RANDOMISATION

Not applicable.

8.3 SAMPLE SIZE

Novel ureteric stent insertion:
50 patients (25 kidney stone patients, 25 oncology patients)

A sample of 50 participants will also allow us to estimate the stent failure rate with a 95% confidence interval (CI) width of approximately +/13%, or approximately +/-18% per arm, sufficient to judge whether the stent is sufficiently safe to progress to further testing. All participants who entered the trial will be included in the analysis of the primary endpoint and its components (intention to treat population). Anyone who consents and/or is registered on the database will be replaced if they do not begin the procedure for insertion of the stent. Those who receive the stent will be included in all other analyses (as-treated population), as these endpoints relate to characteristics of the stent or its use. Loss to follow up is expected to be low, so no adjustment has been made to the sample size. Withdrawal from the study prior to primary endpoint assessment is felt to be unlikely, but we will allow for an additional 3 participants to cover this possibility.

8.4 INTERIM ANALYSIS

No formal statistical testing at an interim stage is planned. For both the kidney stone and oncology cohorts, there will be an assessment of safety after 10 participants have had the stent removed. There is a safety assessment after the 25 kidney stone patients and up to 15 oncology patients have had the stent removed. See section 3.1 for full details.

8.5 STATISTICAL ANALYSIS PLAN (SAP)

The primary analysis will be an estimate of the proportions (and associated 95% Wilson method confidence intervals [21] of stent failure, presented by patient group (oncology or kidney patients). This data will also be compared against data from those using existing stents (UPPEUS); an odds ratio and two-sided 95% confidence interval will be produced for oncology patients and kidney stone patients separately to compare the proportions of stent failure according to stent type. Each element of the composite outcome will also be presented and compared as a secondary analysis, using the same methods as the primary endpoint. The EQ-5D-5L, USSQ, and USI-QoL scores will be summarised with mean, SD, median, and IRQ. No corrections for multiple testing will be applied, and no threshold is set for the p-value as the study is not designed to formally compare groups. Descriptive statistics will be presented for baseline measures and the other secondary outcomes:

- Dwell time (mean, standard deviation) and number of stents required over clinically meaningful period
- Patients who: experience urinary symptoms (for any and for each symptom), use antibiotics, are re-admitted, have urosepsis, die (frequency and percentage)
- Questionnaires at each time point (mean and standard deviation or median and quartiles)
- Laboratory and microbiology data at each time point (mean and standard deviation or median and quartiles)

Adverse events and Serious Adverse Events for the full population will be summarised descriptively for both groups. Overall AEs will be also summarised by CTCAE Grade for each group. No statistical comparisons will be undertaken on this data.

8.6 QUALITATIVE INTERVIEW ANALYSIS

Interview patients:
Until sample saturation (expected up to 30)
Interview clinicians:
Until sample saturation (expected up to 15)

An inductive thematic analysis of the interviews will be conducted [18]. NVivo qualitative data management software will facilitate management of the dataset. Repeated readings of transcripts and listening to recordings will assist familiarisation with the data and identification of initial codes, these will then be defined and guide analysis of the full data set. Using constant comparison, transcripts will be compared within and between each other aiding the iterative search for themes which will then be reviewed, defined and named. Thematic analysis will facilitate the identification of major issues for patients and clinicians and enable relationships between the themes to be developed.

9 REGULATORY COMPLIANCE

9.1 CLINICAL TRIAL AUTHORISATION

This trial has a Clinical Trial Authorisation from the UK Competent Authority the Medicines and Healthcare products Regulatory Agency (MHRA) and a Favourable Research Ethics Committee (REC) Opinion. The trial has been designed in accordance with ISO 14155:2020 and the principles of GCP.

9.2 DEVIATIONS AND SERIOUS BREACHES

9.2.1 Clinical Investigation Plan Compliance

A CIP deviation is any noncompliance with the CIP or Good Clinical Practice (GCP) requirements. Any deviation occurring at sites should be reported to the SCTU and the local R&D Office immediately. As a result of deviations SCTU will advise of and/or undertake any corrective and preventative actions as appropriate. Deviations from the CIP which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

Manufacturers (or SCTU if delegated in the Task Allocation Matrix) must notify the MHRA of all deviations relating to UK study sites as soon as they have been made aware of them. Details about the nature of the deviation, when it occurred, where it occurred, and any proposed corrective and preventative actions should be provided. MHRA provides details on how to report if this, if this is delegated to SCTU, then local processes will be followed.

9.2.2 Serious Breaches

A "serious breach" is a breach which is likely to effect to a significant degree –
- The safety or physical or mental integrity of the participants of the trial; or
- The scientific value of the trial.

All serious CIP deviations/violations and serious breaches of Good Clinical Practice and/or the CIP will immediately be reported to the regulatory authorities and other organisations, as required in the UK Medical Device Regulations 2002, as amended.

9.3 AMENDMENTS/MODIFICATIONS

The Clinical Investigation Plan, Patient Information Sheet, Informed Consent Form and other subject information or other clinical investigation documents (e.g. Instructions for Use) shall be amended as needed throughout the clinical investigation in accordance with local SCTU written procedures for the control of documents and document changes. Proposed amendments to the CIP will be reviewed and authorised locally in accordance with SCTU procedures. Any amendments to the CIP, PIS and ICF shall be notified to the MHRA and REC and will only be implemented once clinical investigation authorisation has been received as per section 9.1.

Local SCTU procedures will be followed in the event that the clinical investigation requires either a temporary halt, or early termination. In the event of early termination of the clinical investigation, there will be no requirement for additional follow-up or continued care for study participants.

10 ETHICAL CONSIDERATIONS

The trial will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the Declaration of Helsinki WMA 64th General Assembly 2013, and recognised by governing laws and EU Directives. Each participant's consent to participate in the trial should be obtained after a full explanation has been given of treatment options, including the conventional and generally accepted methods of treatment. The right of the participant to refuse to participate in the trial without giving reasons must be respected.

After the participant has entered the trial, the clinician may give alternative treatment to that specified in the CIP, at any stage, if they feel it to be in the best interest of the participant. However, reasons for doing so should be recorded and the participant will remain within the trial for the purpose of follow-up and data analysis according to the treatment option to which they have been allocated. Similarly, the participant remains free to withdraw at any time from CIP treatment and trial follow-up without giving reasons and without prejudicing their further treatment.

10.1 RESEARCH ETHICS COMMITTEE REVIEW (REC) AND REPORTS

The Clinical Investigation Plan has received the favourable opinion of a Research Ethics Committee or Institutional Review Board (IRB) in the approved national participating countries.

Within one year after the end of trial, the Chief Investigator will submit a final report with the results, including any publication/abstracts, to the REC.

10.2 SPECIFIC ETHICAL CONSIDERATIONS

Data for this study will be stored on servers located outside of the UK, this is detailed in section 10.4

10.3 INFORMED CONSENT PROCESS

Informed consent is a process that is initiated prior to an individual agreeing to participate in a trial and continues throughout the individual's participation. In obtaining and documenting informed consent, the investigator should comply with applicable regulatory requirements and should adhere to the principles of GCP.

Discussion of objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted are to be provided to the participant by appropriately delegated staff with knowledge in obtaining informed consent with reference to the participant information sheet. This information will emphasise that participation in the trial is voluntary and that the participant may withdraw from the trial at any time and for any reason. The participant will be given the opportunity to ask any questions that may arise and provided the opportunity to discuss the trial with family members, friend or an independent healthcare professional outside of the research team and time to consider the information prior to agreeing to participate.

10.4 DATA PROTECTION AND CONFIDENTIALITY

SCTU will preserve the confidentiality of participants taking part in the study. The investigator must ensure that participant's anonymity will be maintained and that their identities are protected from unauthorised parties. On CRFs participants will not be identified by their names, but by an identification code. Research staff at the treating hospital will enter the data relating to the participants disease and the trial treatment onto an electronic database. The data will be identified by the participants unique trial ID number only. Southampton Clinical Trials Unit are responsible for looking after participants information and using it properly. They will keep participants non-identifiable research data for 25 years after the study has finished.

Non-identifiable data, managed by the Southampton Clinical Trials Unit, will be held on the online clinical trial database software Medidata Rave, as well as the ePRO software (Qualtrics). This software is hosted on secure servers in the EU and the US. Access to this data will be strictly controlled by the Southampton Clinical Trials Unit and no third parties will be granted access to the Medidata servers holding participants research data. All applicable Data Protection legislation will be obeyed by the University of Southampton.

Participant's data will be pseudo-anonymised in order to protect their identity; this means the data will undergo a de-identification procedure where their personal identifiable data (e.g. name, full date of birth) are replaced with one or more artificial identifiers. Therefore, the participants will be referred to solely as this unique reference number for the duration of the trial. This unique reference number will become their participant ID, which will be linked to the audio transcripts. In instances where a participant has consented to the sub study, personal identifiable information will be sent by the site to the qualitative researcher via a secure nhs.net email address. The Patient Identifiable Information will be retained and used by the qualitative researcher to contact the participant and carry out the qualitative interview. Patient identifiable information will include (name, telephone, email address, and/or postal address).

The recordings will be uploaded to a password-protected computer from the recorder and then deleted from the recorder. Audio files will be deleted from the recorder once they have been transcribed verbatim, checked and anonymised. Recordings will be kept on university password-protected servers and secured folders (backup) for up to 10 years after the study completion in case there is a need to check the transcripts or conduct a secondary analysis of the data. Anonymised transcripts of the interviews will be uploaded and kept in the University of Southampton data depository system for at least the recommended 10 years in accordance with the University of Southampton Data Protection policy and for the purpose of data sharing.

11 SPONSOR

SCTU, Chief Investigator and other appropriate organisations have been delegated specific duties by the Sponsor and this is documented in the trial task allocation matrix.

The duties assigned to the trial sites (NHS Trusts or others taking part in this trial) are detailed in the Non-Commercial Agreement.

11.1 INDEMNITY

The University of Southampton's public and professional indemnity insurance policy provides an indemnity to UoS employees for their potential liability for harm to participants during the conduct of the research. This does not in any way affect an NHS Trust's responsibility for any clinical negligence on the part of its staff.

11.2 FUNDING

National Institute for Health and Care Research (NIHR) Invention for Innovation (I4I) Product Development Award (PDA) programme is funding this study.

11.3 SITE PAYMENTS

The payments assigned to the trial sites (NHS Trusts or others taking part in this trial) are detailed in the Non-Commercial Agreement.

11.4 PARTICIPANT PAYMENTS

Participants will not receive payment for participating in the main part of the study. However, participants who consent to take part in the optional qualitative interview will receive a £10 shopping voucher for their time. The voucher can either be emailed to the participant (if digital) or posted to their home address (if they prefer this option, and consent to share their home address).

12 TRIAL OVERSIGHT GROUPS

The day-to-day management of the trial will be co-ordinated through the SCTU and oversight will be maintained by the Trial Management Group (TMG), the Data Safety Monitoring Committee (DSMC), SCTU Director, Sponsor and Funder.

12.1 TRIAL MANAGEMENT GROUP (TMG)

The TMG is responsible for overseeing progress of the study, including both the clinical and practical aspects. The Chair of the TMG will be the Chief Investigator of the study.

The CASSETTE TMG charter defines the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the TMG, including the timing of meetings, frequency and format of meetings and relationships with other trial committees.

12.2 DATA SAFETY MONITORING COMMITTEE (DSMC)

The DSMC will oversee the trial and safeguard the interests of trial participants, monitor the main outcome measures including safety and efficacy, and monitor the overall conduct of the study. If the sponsor/funder has serious problems or concerns with DSMC recommendations, a joint meeting of these groups may be

held. The information shown will depend upon the action proposed and the DSMC's concerns. Depending on the reason for the disagreement, confidential data may have to be revealed to all those attending such a meeting. The meeting will be chaired by a senior member of the SCTU staff or an external expert who is not directly involved with the trial. The CI and member(s) of SCTU are represented on both the TMG and DSMC. Any differences which the TMG and DSMC cannot resolve between themselves will be referred to the sponsor and the funder.

The CASSETTE DSMC charter defines the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the DSMC, including the timing of meetings, frequency and format of meetings and relationships with the TMG.

13 DATA MANAGEMENT

Participant data which is completed on paper will be returned to the SCTU, where it will be entered onto the database by SCTU staff. Other participant data will be entered remotely at site and by participants via a Qualtrics Survey (ePRO) and retained in accordance with the current Data Protection Regulations. The PI, as well as the research staff at site are responsible for ensuring the accuracy, completeness, and timeliness of the data entered.

The participant data is pseudo anonymised by assigning each participant a participant identifier code which is used to identify the participant during the trial and for any participant- specific clarification between SCTU and site. The site retains a participant identification code list which is only available to site staff.

The Participant Information Sheet and Informed Consent Form will outline the participant data to be collected and how it will be managed or might be shared; including handling of all Patient Identifiable Data (PID) and sensitive PID adhering to relevant data protection law.

Trained personnel with specific roles assigned will be granted access to the electronic case report forms (eCRF). eCRF completion guidelines will be provided to the investigator sites to aid data entry of participant information.

Only the Investigator and personnel authorised by them should enter or change data in the CRFs. When requested, laboratory data must be entered by the microbiologist, with all investigator observations entered into the CRF. The original laboratory reports must be retained by the Investigator for future reference.

A Data Management Plan (DMP) providing full details of the trial specific data management strategy for the trial will be available and a Trial Schedule with planned and actual milestones, CRF tracking and central monitoring for active trial management created. Timelines for key tasks will be specified in the DMP and shared with sites during the Site Initiation Visits.

Data queries will either be automatically generated within the eCRF, or manually raised by the trial team, if required. All alterations made to the eCRF will be visible via an audit trail which provides the identity of the person who made the change, plus the date and time.

At the end of the trial after all queries have been resolved and the database frozen, the PI will confirm the data integrity by electronically signing all the CRFs. The CRFs will be archived according to SCTU policy and a PDF copy including all clinical and Meta data returned to the PI for each participant.

Data retention is detailed in section 16 of this CIP.

Data may be requested from the Data Access Committee at SCTU. Any request will be considered on a monthly basis.

14 DATA SHARING REQUESTS FOR RESULTS THAT ARE AVAILABLE IN THE PUBLIC DOMAIN

In order to meet our ethical obligation to responsibly share data generated by interventional clinical trials, SCTU operate a transparent data sharing request process. As a minimum, anonymous data will be available for request from three months after publication of an article, to researchers who provide a completed Data Sharing request form that describes a methodologically sound proposal, for the purpose of the approved proposal and if appropriate a signed Data Sharing Agreement. Data will be shared once all parties have signed relevant data sharing documentation.

Researchers interested in our data are asked to complete the Request for Data Sharing form (CTU/FORM/5219) [template located on the SCTU web site, www.southampton.ac.uk/ctu] to provide a brief research proposal on how they wish to use the data. It will include; the objectives, what data are requested, timelines for use, intellectual property and publication rights, data release definition in the contract and participant informed consent etc. If considered necessary, a Data Sharing Agreement from Sponsor may be required.

15 MONITORING

15.1 CENTRAL MONITORING

Data stored at SCTU will be checked for missing or unusual values (range checks) and checked for consistency within participants over time. Data queries on eCRFs will be raised to site either automatically or manually by SCTU staff via the database. Sites should respond to queries on the database and provide an explanation/resolution to any discrepancies within the required timeframe. Queries and responses are recorded within the database audit trail. There are a number of monitoring features in place at SCTU to ensure reliability and validity of the trial data, which are detailed in the trial monitoring plan.

A copy of the consent form will be sent to the SCTU using the University of Southampton's SafeSend service, to allow for central monitoring. The device accountability document will also be monitored on a regular basis by the Central study team.

15.2 CLINICAL SITE MONITORING

Onsite monitoring will be conducted in accordance with the Trial Monitoring Plan.

15.2.1 Source Data Verification

Upon receipt of a request from SCTU, the PI will allow the SCTU direct access to relevant source documentation for verification of data entered onto the eCRF (taking into account data protection regulations).

The participants' medical records and other relevant data may also be reviewed by appropriate qualified personnel independent from the SCTU appointed to audit the trial, including representatives of the Competent Authority. Details will remain confidential and participants' names will not be recorded outside the trial site without informed consent.

15.3 SOURCE DATA

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

Study-specific source data is described in the Data Management Plan, whilst Source Data Verification (SDV) and the extent to which this will be performed is detailed in the Trial Monitoring Plan. These documents are managed by SCTU according to local procedures.

15.4 AUDITS AND INSPECTIONS

The trial may be participant to inspection and audit by University of Southampton (under their remit as Sponsor), SCTU (as the Sponsor's delegate) and other regulatory bodies to ensure adherence to the principles of GCP, Research Governance Framework for Health and Social Care, applicable contracts/agreements and national regulations.

16 RECORD RETENTION AND ARCHIVING

Trial documents will be retained in a secure location during and after the trial has finished.

The PI or delegate must maintain adequate and accurate records to enable the conduct of the trial to be fully documented and the trial data to be subsequently verified. After trial closure the PI will maintain all source documents and trial related documents. Archiving will be authorised by the Sponsor following submission of the end of trial report. All source and trial related documents will be retained for a period of 25 years following the end of the trial. Recordings of interview transcripts will be kept on university password-protected servers and secured folders (backup) for up to 10 years after the study completion in case there is a need to check the transcripts or conduct a secondary analysis of the data. Anonymised transcripts of the interviews will be uploaded and kept in the University of Southampton data depository system indefinitely for the purpose of data sharing.

Sites are responsible for archiving the ISF and participants' medical records. Following the period of retention, destruction of essential documents will require authorisation from the Sponsor.

The Sponsor is responsible for archiving the TMF and other relevant trial documentation.

17 PUBLICATION POLICY

Data from all centres will be analysed together and published as soon as possible.

Results generated from the analysis of the human samples are owned by University of Southampton.

Individual investigators may not publish data concerning their patients that are directly relevant to questions posed by the trial until the Trial Management Group (TMG) has published its report. The TMG will form the basis of the Writing Committee and advise on the nature of publications. All publications shall include a list of investigators, and if there are named authors, these should include the Chief Investigator, Co-Investigators, Trial Manager, and Statistician(s) involved in the trial. Named authors will be agreed by the CI and Director of SCTU. If there are no named authors then a 'writing committee' will be identified.

We are anticipating publishing trial results in an appropriate open access format.

We aim to generate newsletter(/s) throughout the study about our progress when appropriate. We anticipate creating a short summary (lay language) for clinicians to share with patient participants.

The clinical study paper(/s) will include key findings on removed stents and patients states' from whom samples were removed.

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19 SUMMARY OF SIGNIFICANT CHANGES TO THE CLINICAL INVESTIGATION PLAN

CIP date and version	Summary of significant changes
v1.0 20-May-2024	Original document
V2 – 04-July-2024	Sections 8.1 and 8.3 updated as per MHRA's request
V3 – 06-May-2025	1): Trial schema updated on page 12 of the protocol to include phone call midway through for oncology cohort and 1-3 weeks for all AE's 2): Schedule of events updated in the protocol for both cohorts to include site phone calls to check AEs/DD/s 3): Section 6.5.5 of the protocol updated to include the addition of a site phone call to check for AEs/DDs 4): Section 6.3.3 of the protocol updated to include the addition of a site phone call to check for AEs/DDs 5): Section 6.6.6 of the protocol updated to include the addition of a site phone call to check for AEs/DDs 6): Wording in 7.2.1 updated to reflect addition of follow up phone call 7): Wording in 7.5.1.4 updated to reflect addition of follow up phone call 8): EQ5D-5L questionnaire included at each time point for Kidney stone cohort in section 6.5 9): Section 8.5 added to reflect the addition of EQ5D-5L for the Kidney stone cohort 10): Adjustment to the second questionnaire data point timeline; changing the timing from 24 hours post-surgery 1 to 4–7 days post-surgery 1.Schedule of Observations and Procedures updated in the CIP for both cohorts 11): Section 6.5 and 6.6 updated to reflect that sites can collect questionnaires over the phone if the participant choses this option 12): Trial synopsis, schedule of observations and procedures and sections 2.4 and 2.5 in the protocol have been updated to reflect that the flow study has been moved to the exploratory end point