CaDeT

Multicentre trial of the clinical and cost effectiveness of a novel urinary catheter design in reducing catheter-associated urinary tract infection compared with the traditional Foley design for adults requiring long-term catheterisation (CADET).

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Protocol Information

This protocol describes the CaDeT Trial and provides information about procedures for entering participants. The protocol 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 study, 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 adhere to the principles of Good Clinical Practice (GCP). It will be conducted in compliance with the protocol, the current Data Protection Regulations and all other regulatory requirements, as appropriate.

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LIST OF ABBREVIATIONS

AE	Adverse Event
CAUTI	Catheter Associated Urinary Tract Infection
CI	Chief Investigator
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DMEC	Data Monitoring and Ethics Committee
DMP	Data Management Plan
eCRF	Electronic Case Report Form
eICF	Electronic Informed Consent Form
GCP	Good Clinical Practice
IDMC	Independent Data Monitoring Committee
ISF	Investigator Site File
MHRA	Medicines and Healthcare products Regulatory Agency
MS Teams	Microsoft Teams
NCI	National Cancer Institute
pICF	Paper Informed Consent Form
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCTU	Southampton Clinical Trials Unit
SMS	Text message
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UTI	Urinary Tract Infection

KEYWORDS
Urinary Catheter, Urinary Tract Infection, Catheter Associated Urinary Tract Infection, Bladder Management

1 TRIAL SYNOPSIS

Short title/Acronym:	CaDeT
Full title:	Multicentre trial of the clinical and cost effectiveness of a novel urinary catheter design in reducing catheter-associated urinary tract infection compared with the traditional Foley design for adults requiring long-term catheterisation (CaDeT).

Trial Phase:	Phase III with internal pilot
Population:	Adult long-term indwelling urethral catheter users who have experienced one or more catheter associated UTI in the last 12 months.
Overall Objective:	To determine whether the Optitip catheter provides a clinically and cost-effective alternative to the traditional 'Foley' style catheter for reducing CAUTI and other complications for community dwelling (own home or residential care) adults requiring long-term urinary urethral catheterisation.
Primary Objective:	To assess the clinical effectiveness of the Optitip catheter versus standard Foley catheter design at reducing the incidence of symptomatic UTIs.
Secondary Objectives:	1. To assess the clinical effectiveness of the Optitip catheter versus standard Foley catheter design at reducing catheter related issues, including unplanned catheter change and impact on quality of life. 2. To undertake an economic evaluation to determine the cost effectiveness of the Optitip catheter compared to the standard 'Foley' catheter design. 3. To understand the patient/carer and healthcare professional experience, and the acceptability of the Optitip catheter design.
Rationale:	When normal bladder emptying is not possible due to injury, disease, surgery, or neurological conditions, an indwelling urinary catheter may be required. However, these devices are associated with significant harm and can cause substantial distress for users. Furthermore, managing frequent catheter-associated problems is a resource intensive burden to the providers of community healthcare services[1]. Urinary catheters also have a broader health and societal impact as one of the leading causes of healthcare associated infection and associated use of antimicrobials [3,5]. An estimated 90,000 people in the UK require a long-term (>28 days) urinary catheter. Prevalence increases with age (0.73% in over 70 years, 1.22% over 80), with this increase particularly steep for men. Currently, most catheterised patients use the standard Foley catheter design and experience problems that can constrain work and social lives, including frequent urinary tract infections (UTIs), pain and substantially reduce quality of life. The daily risk of acquisition of bacteriuria when an indwelling

	catheter is in situ is 3–7%. After one month, all users will have bacteria in their urine, which can develop into a UTI[4]. Sixty per cent of users experience one or more catheter associated UTI (CAUTI) per annum and one third experience a UTI at least every 2 months[3]. Long-term catheter users have significantly higher use of antibiotics than non-users[5]. For the healthcare systems supporting the use of catheters, there is a considerable drain on resources. Of all out-of-hours nursing community care, 20% is related to managing catheter blockage[1]. Current strategies and devices designed to reduce harms associated with indwelling urinary catheter use (e.g. addition of coatings, timing of catheter change, the use of bladder washouts) have not proven to be successful[2, 6, 7]. The Optitip catheter design provides features not available in the standard 'Foley' that have the potential to reduce rates of UTI for long-term users. The Optitip is available on the UK drug tariff and, despite the lack of evidence and higher cost of device, it is increasingly being used in the NHS. Therefore, this trial aims to determine whether the Optitip catheter provides a clinically and cost-effective alternative to the traditional 'Foley' style catheter.
Trial Design:	A multicentre randomised controlled superiority trial with two parallel arms, incorporating an internal pilot.
Sample size:	310 (155 per arm)
Intervention:	12 months' use of the novel catheter design – the Optitip catheter.

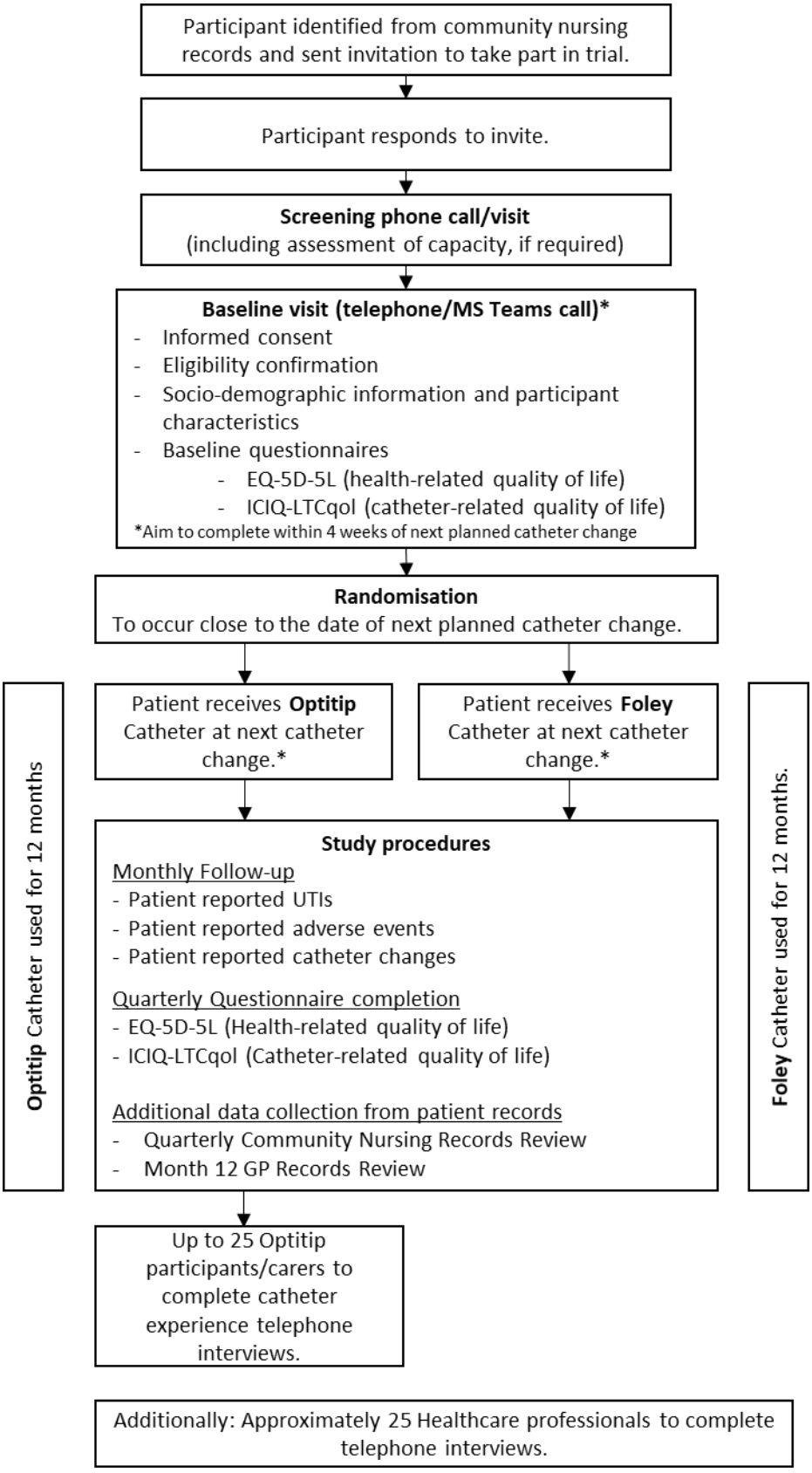
URL for Database:	https://www.imedidata.com
URL for randomisation:	https://prod.tenalea.net/ciru/DM/

Primary Trial Endpoints:	• Number of symptomatic UTIs over 12 months defined as antibiotics prescribed for the treatment of UTI AND at least one of the following symptoms: New or worsening fever, rigors, altered mental status, malaise, flank pain, pelvic discomfort, costovertebral angle tenderness and acute haematuria.
Secondary Trial Endpoints:	• Number of confirmed symptomatic UTIs over 12 months (definition as above) plus microbiological confirmation (10^3 colony-forming units (cfu)/mL of 1 or more bacterial species in a single catheter urine specimen). • UTI versus proportion remaining UTI free (definition as primary) over 12 months • Catheter related quality of life (ICIQ-LTCqol) at 12 months. • Catheter changes (dates and reasons for planned and unplanned changes) over 12 months • Adverse events • Health related quality of life using EQ-5D-5L at 3, 6, 9 and 12 months.

	• Antibiotic use (for any reason) over 12 months. • Within-trial cost effectiveness evaluation of the Optitip catheter against the Foley catheter.
Qualitative Sub-Study	• Patient, carer and healthcare professional experience with Optitip catheter use. • Exploration of motivators and deterrents to trial participation.
Total Number of Sites:	5 NHS Community Trusts in England and up to 2 Health and Social Care Partnerships in Scotland.
Trial duration:	1st June 2021 to 30th November 2024

2 TRIAL SCHEMA

Participant timeline



* The participant's catheter change routine and all other usual catheter associated care (e.g. use of bladder washouts) will remain unchanged

3 SCHEDULE OF OBSERVATIONS AND PROCEDURES

	Screening/ Registration	Baseline	Randomisation	Follow-up Month (Day 0 = Date of randomisation)												End of study
				1	2	3	4	5	6	7	8	9	10	11	12	
Pre-screening and invitation	X															
Screening phone call/visit (including assessment of capacity, if required)	X															
Informed Consent		X														
Confirmation of Eligibility		X														
Participant Characteristics		X														
Socio-demographic information		X														
Medical History		X														
Questionnaire completion - EQ-5D-5L - ICIQ-LTCqol		X				X			X			X			X	
Contact Details		X														
Randomisation			X													
Intervention/control catheter*				X	X	X	X	X	X	X	X	X	X	X	X	
Collection of monthly patient reported UTIs and Adverse Events (primary and secondary definitions)				X	X	X	X	X	X	X	X	X	X	X	X	
Quarterly Community Nursing Records Review						X			X			X			X	
GP Records Review																X
Qualitative interviews (up to 25 patients/carers and 25 healthcare professionals)																X**

***** The participant's catheter change routine and all other usual catheter associated care (e.g. use of bladder washouts) will remain unchanged.

** Participants on the Optitip arm can be interviewed from Month 9 to the end of the study or at the point of withdrawal for participants that cease trial participation before month 9.

NB: The Participant 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 has specifically stated that they do not want this to happen).

4 INTRODUCTION

4.1 BACKGROUND

When normal bladder emptying is not possible due to injury, disease, surgery, or neurological conditions, an indwelling urinary catheter may be required. However, these devices are associated with significant harm and can cause substantial distress for users. Furthermore, managing frequent catheter-associated problems is a resource intensive burden to the providers of community healthcare services[1]. Urinary catheters also have a broader health and societal impact as one of the leading causes of healthcare associated infection and associated use of antimicrobials[3, 5].

An estimated 90,000 people in the UK require a long-term (>28 days) urinary catheter. Prevalence increases with age (0.73% in over 70 years, 1.22% over 80), with this increase particularly steep for men. Overall, a higher proportion of patients have a neurological (vs. non-neurological) reason for catheter use (62.9% vs. 37.1%) and use urethral (vs. suprapubic) catheters (59.7% vs. 40.3%). Compared to men, more women tend to use suprapubic catheters (56.4% vs. 29.3%) and have a catheter for neurological reasons (71.8% vs. 56.2%) [8].

Currently, most catheterised patients use the standard Foley catheter design and experience problems that can constrain work and social lives, including frequent urinary tract infections (UTIs), pain and substantially reduce quality of life. The daily risk of acquisition of bacteriuria when an indwelling catheter is in situ is 3–7%. After one month, all users will have bacteria in their urine, which can develop into a UTI[4]. Sixty per cent of users experience one or more catheter associated UTI (CAUTI) per annum and one third experience a UTI at least every 2 months[3]. Long-term catheter users have significantly higher use of antibiotics than non-users[5]. Recent research has demonstrated that the majority of people with antibiotic resistant bacteria acquire their resistance in the community, suggesting that efforts to reduce antibiotic use should focus on community settings[9]. For the healthcare systems supporting the use of catheters, there is a considerable drain on resources. Of all out-of-hours nursing community care, 20% is related to managing catheter blockage [1]. Notwithstanding the health issues related to indwelling catheters, these devices can give essential control over bladder drainage that other methods of management (e.g. absorbent pads, intermittent catheters) might not provide. Indeed, indwelling catheters are now one of the most commonly used long-term medical devices.

Current strategies and devices designed to reduce harms associated with indwelling urinary catheter use (e.g. addition of coatings, timing of catheter change, the use of bladder washouts) have not proven to be successful[2, 6, 7]. In an address at the bi-annual Innovating for Continence 2011 conference, leaders in the field of catheter research Professors Feneley, Kunin and Stickler stated that "The placement of the Foley catheter in the bladder undermines the important defences of the urinary tract against infection. The morbidity induced in many elderly and disabled people undergoing long-term catheterisation and the costs to health services of dealing with the problems are not acceptable in the twenty first century"[10].

There has been little innovation in indwelling catheter design for the last 80 years. With the introduction of latex in the 1930s, Foley and Belnap designed a flexible, double channelled balloon indwelling catheter that is similar to devices commonly used today[11]. Since then a small number of devices with novel design features aimed at reducing CAUTI (and other harms) have become available but lack an evidence base or assessment of cost effectiveness[12].

There is considerable desire on behalf of both catheter users and clinicians to reduce the burden of catheter use, but the lack of progress in this area is well reported[11, 12]. This frustration has led to the rapid and widespread adoption of novel and costly catheters that have subsequently proven to be no more effective against UTI than cheaper standard 'Foley' devices. One example of this phenomena was the substantial expenditure on silver coated catheters that (despite largely positive laboratory and early clinical studies) were found to be no more beneficial than 'Foley' devices with regards to occurrence of UTI[13].

4.2 RATIONALE AND RISK BENEFITS FOR CURRENT TRIAL

4.2.1 The Optitip Catheter

A review of globally available novel indwelling urinary catheter designs was undertaken. The Optitip was agreed to have the most potential to both reduce rates of UTI for long-term users and be cost effective.

The Optitip is available on the UK drug tariff and, despite the lack of evidence and higher cost of device (£10.95 vs around £3 for the standard 'Foley'), it is increasingly being used in the NHS, with its perceived advantages spread by word of mouth (both by healthcare professionals and catheter users). Launched in 2017, usage has risen from 238 in the first year to 5328 from Apr 2019 to Mar 2020 (Sources: NHS Digital Prescription Cost Analysis & Linc Medical). The team considers that the Optitip design provides features not available in the standard 'Foley' that have the potential to reduce rates of UTI for long-term users. Table 1 presents the principles underpinning the rationale for the choice of the Optitip catheter, and a comparison of the Standard 'Foley' and Optitip catheters in relation to these principles. The Optitip catheter is inserted and removed in the same way as the standard 'Foley' catheter, and requires no specific training.

Principle	**Standard 'Foley' (Figure in Appendix 1)**	**Optitip (Figure in Appendix 1)**
1. To be effective and avoid harm, indwelling urinary catheters must drain the bladder effectively at low pressure, allowing complete emptying. It is hypothesised that having a 'sump' of urine at the base of the bladder that is not effectively drained provides a reservoir for microbes	Drainage port is above the balloon, leaving a 'sump' of urine at the base of the bladder.	Has an additional drainage port below the balloon to reduce the 'sump'.
2. Negative pressure, which can occur in the catheterised bladder, can cause the bladder mucosa to be sucked into the drainage eyelets causing bleeding, inflammation, pain, blockage and haemorrhagic pseudopolyps. It is hypothesised that this can increase the risk of CAUTI.	Only one drainage port which can get blocked by bladder mucosa.	Has two drainage ports reducing the likelihood of developing negative pressure due to blockage.
3. Protrusions can damage the bladder mucosa causing pain and are hypothesised to increase the risk of CAUTI.	Has a protruding tip which has been demonstrated to damage the mucosa.	Has an open drainage port at the top that protrudes less than a standard 'Foley' catheter tip.

Table 1. Choice rationale principles

4.2.2 Rationale for the trial

As previously noted, long-term catheter use is associated with significant harm, and is a resource intensive burden to the providers of community healthcare services. The lack of progress in this area has led to the rapid adoption of novel and costly cathers that have subsequently proven to be no more effective against CAUTI than standard 'Foley' devices.

The Optitip catheter is CE marked, and is increasingly being used in the NHS, despite the lack of evidence and higher cost of device. Robust evidence of clinical and cost effectiveness is imperative to inform future recommendations.

We do not know whether the intervention catheter will be more effective than the standard design. However, it is possible that participants experience a reduction in number of UTIs or other catheter related harms. For

all participants, the high level of monitoring for UTI may result in better-targeted treatment and added catheter-related vigilance in general.

5 TRIAL OBJECTIVES

	Objective	Endpoint(s) used to evaluate
Primary:	To assess the clinical effectiveness of the optitip catheter versus standard Foley catheter design at reducing the incidence of symptomatic UTIs.	Number of symptomatic UTIs over 12 months defined as antibiotics prescribed for the treatment of UTI AND at least one of the following symptoms: New or worsening fever, rigors, altered mental status, malaise, flank pain, pelvic discomfort, costovertebral angle tenderness and acute haematuria.
Secondary:	1. To assess the clinical effectiveness of the Optitip catheter versus standard Foley catheter design at reducing catheter related issues, including unplanned catheter change and impact on quality of life.	• Number of confirmed symptomatic UTIs over 12 months (definition as above) plus microbiological confirmation (10^3 colony-forming units (cfu)/mL of 1 or more bacterial species in a single catheter urine specimen). • UTI versus proportion remaining UTI free (definition as primary) over 12 months • Catheter related quality of life (ICIQ-LTCqol) at 12 months. • Catheter changes (dates and reasons for planned and unplanned changes, including dwell time) over 12 months • Adverse events e.g. (pain, blockage, spasm)
	2. To undertake an economic evaluation to determine the cost effectiveness of the Optitip catheter compared to the standard 'Foley' catheter design.	• Health related quality of life using EQ-5D-5L at 3, 6, 9 and 12 months. • Antibiotic use (for any reason) over 12 months. • Within-trial cost effectiveness evaluation of the Optitip catheter against the Foley catheter.
Qualitative interviews	3. To explore patient, carer and healthcare professional experience with Optitip catheter use 4. To explore motivators and deterrents to trial participation.	• Telephone/MS Teams interviews with a purposive sample of up to 15 trial participants, 15 participants who declined the trial, and up to 2 healthcare professionals from each community trust. Framework analysis will be used to address specific catheter questions.

6 TRIAL DESIGN

A multicentre randomised controlled superiority trial with two parallel arms to assess the clinical and cost effectiveness of the Optitip catheter design, compared to the standard 'Foley' design. Patients will be randomised to receive: A) Optitip or B) standard 'Foley' catheters, each according to their manufacturer's guidance for use for a 12-month period.

Patients will be randomised in a 1:1 ratio through a web-based system using a minimisation algorithm incorporating a random element. Factors used for minimisation will be gender, use of prophylactic antibiotics at baseline, number of average annual UTIs at baseline (less than 4/4 or more), location (own home/residential care), and Trust/Partnership.

The trial will include a 6-month internal pilot with clear stop-go criteria based on recruitment rates and data completeness:

Criteria assessed at 6 months	% Threshold		
	Red	Amber	Green
Trial recruitment	<80%	>80%, <100%	100%
Mean recruitment rate/ site/ month	< 2.5	>= 2.5, < 3	>= 3
Number of sites opened	<5	5-6	All (7)
Total number of participants recruited	< 80	>= 80, < 94	>= 94
UTI report data (primary outcome) completeness	< 80	>= 80, < 90	>= 90

Actions:

- Red: Trial probably cannot be delivered, discuss closure with Trial Steering Committee (TSC).
- Amber: Identify and address issues; develop recovery plan with TSC & Funder, review.
- Green: Continue

6.1 TRIAL ENDPOINTS

6.1.1 Primary endpoint

Number of symptomatic UTIs over 12 months defined as antibiotics prescribed for the treatment of UTI AND at least one of the following symptoms: New or worsening fever, rigors, altered mental status, malaise, flank pain, pelvic discomfort, costovertebral angle tenderness and acute haematuria.

6.1.2 Secondary endpoints

- Number of confirmed symptomatic UTIs over 12 months (definition as above) plus microbiological confirmation (10^3 colony-forming units (cfu)/mL of 1 or more bacterial species in a single catheter urine specimen).
- UTI versus proportion remaining UTI free (definition as primary) over 12 months
- Catheter related quality of life (ICIQ-LTCqol) at 12 months.
- Catheter changes (dates and reasons for planned and unplanned changes) over 12 months
- Adverse events
- Health related quality of life using EQ-5D-5L at 3, 6, 9 and 12 months.
- Antibiotic use (for any reason) over 12 months.
- Within-trial cost effectiveness evaluation of the Optitip catheter against the Foley catheter.

6.1.3 Qualitative endpoint

- Telephone/MS Teams interviews with a purposive sample of up to 15 trial participants, 15 participants who declined the trial, and up to 2 healthcare professionals from each community trust who have delivered the intervention to explore patient, carer and healthcare professional experience with Optitip catheter and motivators and deterrents to trial participation. Framework analysis will be used to address specific catheter questions.

6.2 DEFINITION OF END OF TRIAL

End of trial and end of study are defined as the date when the last point of data is collected for the last participant from the follow-up interviews.

7 SELECTION AND ENROLMENT OF PARTICIPANTS

7.1 CONSENT

Consent to enter the trial must be sought from each participant only after a full explanation has been given.

The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the trial the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases, the participants remain within the trial for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

Consent will be obtained using remote eConsent or remote paper consent methods, as outlined below.

7.1.1 Remote eConsent

Participants will be provided access to the Participant Information Sheet on the trial website, and time allowed for consideration. Remote online participant eConsent will be obtained using the trial consent website. The patient will be guided through the consent process via a phone call/MS Teams Call with an appropriately trained site/hub researcher. Once the patient has signed consent, the consenter will also use the trial consent website to electronically sign the electronic informed consent form (eICF). A record of the phone call should be made in the patient's notes. When consent is completed by hub staff, a record of the phone call should be sent to site for inclusion in the patient's notes. Upon completion of the online eICF, an automatic email providing a link to the completed eICF (within the secure trial consent website) will be sent to the participant; the site (who will print and file copies in the participant's medical notes and in the ISF); the recruitment hub; and the SCTU trial mailbox.

Potential participants can be supported by carers/family members/others to use the eConsent system as appropriate.

7.1.2 Remote paper consent

The patient will be provided a copy of the paper Informed Consent Form to complete at home. The patient will be guided through the consent process via a phone call/MS Teams call with an appropriately trained site/hub researcher. The site member must make a note of the call in the patient's notes. When consent is completed by hub staff, a record of the phone call should be sent to site for inclusion in the patient's notes.

Upon completion of the Informed Consent Form the patient will post the consent form to the site/hub in the addressed, freepost envelope provided. Once received by the site/hub, this must be counter-signed by the staff member who took consent, the original consent form is to be kept in the site ISF. Three copies of the ICF should be made: one copy should be returned to the patient, one copy is to be kept in the participant's medical notes and one copy of the consent form will be sent to the SCTU, with consent from the participant, via email to uhs.sctu@nhs.net using a secure nhs.net email address, or using the University of Southampton SafeSend service, to allow for central monitoring.

7.1.3 Consent for Qualitative Interviews

All participants will be asked for consent to be contacted about the qualitative interviews, this is optional and is not required to take part in the main trial. Participants will also give consent for their contact details to be shared with the qualitative researcher. The contact details will be accessed securely by the researcher who will contact these participants directly by telephone/MS Teams call. Healthcare professionals who deliver the intervention will be asked to register interest in taking part in the qualitative interviews. Participants/healthcare professionals agree to be interviewed, verbal consent will be taken over the

telephone/video call by the researcher before starting the interview and will be recorded using a digital audio recording device.

8 INCLUSION CRITERIA

1. Aged 18+
2. Community dwelling (own home or residential care, including assissted living)
3. Use of an indwelling urethral catheter (for any reason) for 28 days or more and anticipated to continue with catheterisation for 1 year or more.
4. Experienced one or more catheter associated UTIs in the last 12 months
5. Willing to be randomised to either study arm
6. Willing and able to give informed consent

9 EXCLUSION CRITERIA

7. Current therapy for bladder cancer
8. Under surveillance follow-up for previous bladder cancer
9. Current interventional therapy for prostate cancer
10. Previous bladder radiotherapy
11. Unresolved urethral stricture or bladder neck stenosis
12. Traumatic hypospadias
13. Terminally ill
14. Otherwise deemed unsuitable for trial

Pregnant women are **not** excluded from the trial. Details of the pregancy should be recorded, with consent, on the Pregnancy report CRF.

Co-enrollment in other trials is permitted with approval from the Chief Investigator (CI).

10 SCREENING FAILURES

Potential participants who are screen failures (i.e. do not complete a baseline visit because they are not eligible for the trial) will be documented in the site screening log, together with reasons for exclusion. The screening log will be filed in the Investigator Site File.

11 REGISTRATION/RANDOMISATION PROCEDURES

11.1 REGISTRATION AND RANDOMISATION PROCEDURES

In each site, participants who meet the eligibility criteria for the trial, and for whom written informed consent has been obtained will be assigned a Patient Identifier Number. This will be the Site ID, combined with an auto-generated Patient Number taken sequentially from a list provided to sites.

The recruiting site will inform the SCTU by scanning and emailing through the Eligibility/Registration Form to the SCTU within 24 hours of registration to cadet@soton.ac.uk.

In each site, participants who meet the eligibility criteria for the trial, and for whom written informed consent has been obtained will be individually randomised in a 1:1 ratio to either the intervention or control. Participants should be randomised as close to the date of their next planned catheter change as possible, allowing time for the trial catheter to be delivered to the patient.

Patients will be randomised in a 1:1 ratio through a web-based system using a minimisation algorithm incorporating a random element. Factors used for minimisation will be gender, use of prophylactic antibiotics at baseline, number of average annual UTIs at baseline (less than 4; 4 or more), location (own home/residential care), and Trust/Partnership. Patients will be informed of allocation prior to their next catheter change.

Once a patient has been randomised to the trial, the web-based system will send an email (without allocation information) to SCTU/Glasgow hub. Sites will receive an email from the web-based system with the allocation information.

Because the external portion of the catheters vary between the Optitip and 'Foley' catheter, participants will not be blind to allocation. All co-ordinating centre/recruitment hub staff and site staff will not be blinded to catheter allocation to ensure the correct catheter is prescribed for participants, and to capture catheter change information.

11.2 CONTRACEPTION

There are no contraception stipulations as part of the trial and participants may continue to use their usual methods of contraception while taking part in the study. If a participant is/becomes pregnant during the trial this should be recorded (with the participant's consent) on the pregnancy report form on the electronic database and will be reported to sponsor by SCTU.

12 TRIAL OBSERVATIONS AND PROCEDURES

12.1 SCREENING PROCEDURES

12.1.1 Pre Screening

Participating sites will conduct a search of their patient database or electronic/paper records. The search will specifically look for adults with an indwelling urethral catheter who are anticipated to continue with catheterisation for 1 year or more. History of a UTI in the last 12 months can be included in the search, however there may be discrepancies between local definitions for UTIs compared to the trial definition. This should be covered in the screening phone call and eligibility assessment (see section 12.1.2, below).

Patients can be approached via SMS/postal invite, or will be approached during usual face-to-face visits.

SMS messages will be sent from the clinical site team, where possible, using the Patient Invitation text template. Text messages will be sent using the Textanywhere system so patients are able to identify who is messaging them. Messages will provide a link to the trial website, and contact details for the site team. Sites who are unable to use this system should send the initial approach via postal invite, or approach patients during their usual face-to-face visits.

The paper trial pack will include, on local headed paper: an invitation letter informing potential patients about the trial, with a link to the trial website, a paper copy of the PIS, reply slip, and contact details for the site team. Letters will be sent according to local procedures, or by using DocMail which is a standards-compliant hybrid mail service, providing document management and ISO 27001 secure mailings.

Patients being approached during usual face-to-face visits and will be given an invitation letter (including a link to the trial website), PIS and reply slip.

Patients will then have the opprotunity to consider whether they would like to particpate in the trial. Patients will be able to contact the site to ask questions about participating in the trial.

One attempt will be made to contact non-responders to the invite, within a minimum of 3 weeks after they have been invited to participate in the trial. This will eitehr be a telephone call (with a pre-text) which will be carried out by the clinical care team or the research team (after verbal consent to allow this) or sending out a reminder letter. The site research team will discuss the trial and to give the patient an oppurtunity to ask questions. A record of the type of reminder will be logged on the screening log at site.

Patients can register their interest in taking part using the trial website/by contacting the site team/ returning their reply slip.

Patients who have registered interest in taking part will be contacted by the site/recruitment hub. For those who do not wish to take part, the trial website and the reply slip will have some common reasons for non-particpation, which can be completed on the website or posted to the site/recruitment hub in the pre-paid envelope, if they so wish.

Those who have declined the trial and wish to complete the reply slip can consent to be contacted to take part in an interview to explore motivators and deterrents to trial participation. Additionally, anonymised notes from the coordinating centre (Southampton Clinical Trials Unit, and Glasgow Clinical Trials Unit) about barriers and facilitators to trial implementation and participant recruitment will be analysed.

The SCTU team will raise the awareness of the trial in the patient and nursing community, using social media platforms such as Facebook and Twitter/ X. Social media advertisements will include a link for the patient to click on to register their interest in the trial. A link to the patient information sheet will also be provided. Other social media platforms will be explored and utilised where needed. We will use regional advertisements, to target areas across England and Scotland, where the trial is being conducted. Additionally, recruitment posters will be displayed in clinic settings (such as urology clinics), at participating sites, to raise awareness of the trial.

12.1.2 Screening

After a participant has expressed interested in taking part in the trial the research team will conduct a screening phone call. The exception to this will be if there are any circumstances (e.g. communication difficulties) which make it challenging to undertake this appointment by telephone, in which case a face-to-face appointment will take place in the participant's home.

This will involve assessing the patient's potential eligibility based on information obtained in routine care, alongside that provided on the reply slip, or as reported by the patient during the screening phone call.

If the participant is potentially eligible and wishes to participate, a baseline telephone appointment will be arranged with a Trust/Partnership/Hub Research Nurse/other qualified and delegated Healthcare Professional. This can be completed at the same time as the screening phone call/visit where possible (see Section 7.1 for Consent methods).

After Informed Consent has been given at the baseline call/visit eligibility will be confirmed and recorded on the CRF by the Trust/Partnership/Hub Research Nurse, or other qualified and delegated Healthcare Professional.

12.1.3 Assessment of Capacity

Where there is a concern that an individual lacks capacity (e.g. based on patient notes review, or concern during the consent process) to provide informed consent for themselves to participate in the trial they will be assessed for capacity by the Research Nurse/Community Nurse/other qualified and delegated Healthcare Professional and through this they will be deemed capable or incapable of giving informed consent. The assessment will be completed according to HRA guidance (https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/mental-capacity-act/). The outcome of the assessment will be recorded on the relevant pCRF/eCRF.

12.1.4 COVID-19 Considerations

Remote consent methods should be used wherever possible.

If COVID-19 related restrictions are in place that prevent additional in-person visits, patients who require these (e.g. due to communication difficulties) will not be approached for participation in the trial until

restrictions are lifted. Patients who have registered interest should be informed of this. Patients who are approached for trial participation at their usual visits can still be approached in this way. All follow-up visits are to be completed remotely.

13 TRIAL PROCEDURES

All procedures to be completed via telephone, or MS Teams call, wherever possible.

- Pre-screening Assessment
- Screening phone call/visit*
- Baseline phone call/visit*
    - Informed consent
    - Confirmation of Eligibility
    - Participant Characteristics
    - Socio-demographic information
    - Medical History
    - Questionnaires
        - EQ-5D-5L
        - ICIQ-LTCqol
    - Contact Details
- Randomisation

*Screening and baseline phone calls/visits can be completed at the same time, if appropriate.

Catheters will be issued or delivered to participants following consent, confirmation of eligibility, and randomisation. Catheter allocation should be recorded on the participants's community nursing record so that the Community Nurses completing the participant's catheter change are aware of which catheter should be used. Once randomised, participants will receive either the intervention or their usual catheter at their next catheter change and will continue to receive that catheter for a period of 12 months. The 12-month intervention period will start on the date of the catheter change.

Control participants will continue to receive their usual 'Foley' catheters as per local procedures. For participants randomised to intervention, sites will arrange for a stock of the Optitip catheter to be provided to each participant at the start of the trial based on their usual usage (e.g. 4 per year or 12 per year) plus two spare devices. At some sites GPs will be responsible for prescribing the catheter.

The participant's catheter change routine and all other usual catheter associated care (e.g. use of bladder washouts) will remain unchanged. Regular catheter care will be provided by community nurses according to local procedures. No specific training is required for the use of Optitip catheters.

Participants will be sent a Participant Diary from the Co-ordinating Centre/Recruitment Hub to be used as an aide memoir for recording UTI symptoms, antibiotic use, and dates of catheter changes.

13.1.1 Pre-screening

See Section 12.1.1.

13.1.2 Screening

See Section 12.1.2.

13.1.3 Informed Consent

See section 7.1.

13.1.4 Baseline Phone Call/Visit

To be completed by Site/Hub researcher. The eConsent process can be completed at the start of the baseline phone call/visit. Where remote paper consent is used, the consent form must be received by the site prior to the baseline phone call/visit.

Sites should aim to complete the baseline call/visit within 4 weeks of the participant's next planned catheter change, where possible.

Participant Characteristics

The relevant participant characteristics to be recorded as the baseline call or visit are:

- Gender
- Age
- Ethnicity
- Reason for catheter use
- Time with catheter
- Independence with activities of daily living (Barthel Index)

Socio-demographic information

The relevant socio-demographic information to be recorded as the baseline call or visit is:

- Living situation
- Employment status

Medical History

The relevant medical history to be recorded as the baseline call or visit is:

- History of previous catheter use
- Concomitant Medications, only including the below:
    - Antibiotics (any reason for use, including antibiotics unrelated to treatment of UTIs, or prophylactic antibiotics)
    - Antimuscarinics
    - Anticholinergics
    - Buscopan
    - Bladder washouts/Suby G
    - Mirabegron
    - Other catheter related medication (including topicals)

Questionnaires

Interviewer to administer questionnaires over the phone, and record responses on the eCRF. Questionnaires can also be completed using the secure online platform or via post, if required. Questionnaires to be administered are:

- EQ-5D-5L
- ICIQ-LTCqol (ICIQ Long-term Catheter quality of life)

Contact details

Patient contact details and contact details of their GP will be collected from all participants to enable monthly follow up and facilitate the GP notes review at the end of the study. Participants will be asked for their preferred follow-up method (online form/telephone follow-up/postal). Participants will be asked for their preferred communication method for notifications relating to follow-up (phone call/text/email (emails to be sent by site, or by hub using the University of Southampton's Safesend service)). The participant contact details will be recorded by the participant on the trial website along with their consent for this information to be used for trial purposes when the patient completes the registration form on the eConsent platform. Participants who complete the paper consent process will provide their contact details on the paper Contact Details form. GP contact details for all patients will be recorded on the paper Contact details form. Once the

Contact details form was completed, the hub team (at GCU or SCTU) will enter the patient's and GP details in the eConsent platform.

13.1.5 Randomisation

See section 11. The participant should be randomised as close to their next planned catheter change as possible.

13.1.6 GP Letter

A letter will be sent to the participant's GP informing them of their patient's participation.

13.2 FOLLOW UP

The below data will be collected from multiple sources to reduce amount of missing data:

- UTI (primary definition)
    - Defined as antibiotics prescribed for the treatment of UTI AND at least one of the following symptoms: New or worsening fever, rigors, altered mental status, malaise, flank pain, pelvic discomfort, costovertebral angle tenderness and acute haematuria
    - The primary data source is patient reported UTIs. This will be supplemented by data from GP records and community nursing records.
    - Symptoms may not be fully recorded in GP notes. Additionally, many catheter users experience frequent UTIs, and some keep a supply of 'just in case' antibiotics at home.

- UTI (secondary definition)
    - Defined as for primary definition plus microbiological confirmation (10^3 colony-forming units (cfu)/mL of 1 or more bacterial species in a single catheter urine specimen).
    - For each symptomatic UTI (whether participant/GP/community nursing reported), the GP records will be reviewed to check whether the infection was microbiologically confirmed (defined as 10^3 colony-forming units (cfu)/mL of 1 or more bacterial species in a single catheter urine specimen). This will be supplemented by data from community nursing records (where this is available in records).
- Antibiotic use (for any reason)
    - Antibiotic use (for any reason) will be gathered for each participant from three sources (patient reported, community nursing records, GP records). This will be collated and cross checked to remove duplication and overlap.
- Concomitant Medications
    - Specified concomitant medications (see section 13.2.3) will be gathetered from community nursing records and GP records. These will be collated and cross checked to remove duplication and overlap.
- Catheter changes
    - Catheter changes (including unplanned changes due to blockage, infection or accidental dislodgement) could take place in the community, in an 'out of hours' service, GP practice or acute care. Therefore, data will be collected from both community (or nursing home) records (quarterly through the intervention period) and from the participant (during monthly follow-up).
- Catheter related healthcare service use
    - Catheter-related service use and supplies will be gathered for each participant from three sources (community nursing records, GP records, nursing home records (if applicable)). This will be collated and cross checked to remove duplication and overlap.
- Adverse Events
    - Participants will be asked to contact the site team at the time of the event and additionally will be asked during monthly follow-up if they have experienced any adverse events that they think are related to their catheter, or any SAEs (related or unrelated to catheter use). When an SAE occurs, participants' GPs will be contacted to obtain further data on the SAE, where required (participants will consent to this at baseline). Data on participant reported

SAEs/AEs will also be supplemented from community nursing notes that will be searched quarterly. All SAEs to be handled in accordance with Section 14.5.

13.2.1 Monthly participant reported UTIs, catheter changes, antibiotic use, and Adverse Events

Monthly follow up to be completed by the co-ordinating centre/hub using the participant's choice of online form/telephone follow-up/postal. Follow-up prompts for the collection of self-reported data to be sent using the participant's contact preference choice, using the appropriate template wording. If a participant does not respond after one week a reminder will be sent using the same contact method. If a response is not received after one more week the participant will receive a telephone reminder and the data will be collected over the telephone.

This will be completed every month for the 12-month intervention period.

Other methods may be implemented by the SCTU and GCU hub, in effort to increase the response rate and to improve patient retention by reducing the patient burden of monthly telephone calls and postal returns. This includes sending the monthly follow ups to the patient quarterly, so that patients can receive month 1, 2 and 3 follow ups at month 1, and only return to the research team/ complete over the telephone or online, at the end of the 3-month reporting period. A similar approach will be taken for the follow up for months 4, 5 and 6; months 7, 8 and 9; and months 10, 11 and 12.

Sites will be sent a copy of the data using SafeSend, which should be filed in their ISF.

Symptomatic UTI (primary and secondary definition)
The participant will be asked if they have experienced a UTI. If they have experienced a UTI in the previous month, the research team will record the details on a pro forma.

Adverse Events
Participants will be asked if they have experienced any adverse events that they think are related to their catheter. This will also be an opportunity for participants to raise any concerns or queries.

All Adverse Events, including unreported SAEs, will be reported to the site by the co-ordinating centre/hub. The site should report AEs and SAEs following procedures in Section 14.5.

Antibiotic use
Participants will be asked if they have used antibiotics for any reason. This includes antibiotic use which is unrelated to the participant's catheter use.

Catheter changes
Participants will be asked if they have had their catheter changed in the last month. If they have had a catheter change, the research team will record the details on a pro forma.

13.2.2 Quarterly Questionnaire Completion

At months 3, 6, 9 and 12 the participant will be asked to complete questionnaires in addition to their usual monthly follow-up. The following questionnaires will be administered via the same method as the participant's monthly follow-up (online form/telephone/post), unless the participant requests to complete questionnaire using another method:

- EQ-5D-5L
- ICIQ-LTCqol

Sites will be sent a copy of the questionnaires using SafeSend, which should be filed in their ISF.

13.2.3 Quarterly Community Nursing Records Review

Community nursing records to be reviewed at the end of the intervention period (month 12) and at intervention months 3, 6 and 9. The review will record:

- UTI according to primary and secondary definitions (if captured in community nursing records)
    - UTI date
    - UTI symptoms
    - Antibiotic prescription and reason (any reason for antibiotic prescription to be recorded)
    - Microbiological confirmation of UTI
- Concomitant Medications, only including the below:
    - Antimuscarinics
    - Anticholinergics
    - Buscopan
    - Bladder washouts/Suby G
    - Mirabegron
    - Other catheter related medication (including topicals)
- Catheter changes
    - Date of change
    - Reason for change (including planned/unplanned)
    - Confirmation of which catheter type was used
- Catheter related supplies (if captured in community nursing records)
    - Catheters
    - Washout solutions
    - Draining bags
    - Valves
    - Other catheter related supplies
- Catheter related healthcare service use
    - Bladder washouts
    - Other catheter-related community service use (e.g. visits to check catheter positioning, catheter-related pain etc.)
- Adverse events

If the participant lives in a residential care home with nursing care, the catheter related activity will be similarly recorded.

The review should be completed within 1 month of the end date for the review period, wherever possible.

If the participant is changed from the allocated catheter due to clinical judgement, the new catheter and reasons for the change should be recorded on the eCRF.

13.2.4 GP Records review

GP records to be reviewed at the end of the 12-month intervention period. The review will record:

- UTI according to primary and secondary definitions:
    - UTI date
    - UTI symptoms
    - Antibiotic prescription and reason (any reason for antibiotic prescription to be recorded)
    - Microbiological confirmation of UTI
- Catheter related supplies
    - Catheters
    - Washout solutions
    - Draining bags
    - Valves
    - Other catheter related supplies
- Catheter related healthcare service use

- GP contacts
- A&E attendances
- Other hospital care
- Other primary/community healthcare service use
- Medications, only including the below:
    - Antibiotics (any reason for use, including antibiotics unrelated to treatment of UTIs, or prophylactic antibiotics)
    - Antimuscarinics
    - Anticholinergics
    - Buscopan
    - Bladder washouts/Suby G
    - Mirabegron
    - Other catheter related medication (including topicals)

- Electronic Frailty Index (where available)

If the participant is changed from the allocated catheter for any reason, the new catheter and reasons for the change should be recorded on the eCRF.

13.2.5 Arrangements for continued provision of the intervention for participants after trial participation ends

If participants would like to continue/start using the intervention catheter (Optitip) at the end of their participation in the trial, they will be advised to speak with a member of their care team responsible for prescribing thei catheter (GP or community nursing team) to discuss this. The Optitip catheter is currently available on the UK drug trariff, however, there may be local variation on availability.

13.2.6 Qualitative Interviews

Telephone/MS Teams interviews will be conducted with up to 15 trial participants, up to 2 healthcare professionals from each community trust, and 15 patients who declined the trial participants/carers (purposive sample, with a balance of male and female participants from across the recruitment hubs) and up to 2 healthcare professionals (purposive sample, with a balance of participants from across the recruitment hubs) who have received/delivered the intervention. Framework analysis will be used to address specific catheter questions.
Consenting participants on the Optitip arm can be interviewed from month 9 to the end of the study or at the point of withdrawal for participants that cease trial participation before month 9.

13.3 DEVIATIONS AND SERIOUS BREACHES

Any Trial protocol deviations/violations and breaches of Good Clinical Practice occurring at sites should be reported to the SCTU and the local R&D Office immediately. SCTU will then advise of and/or undertake any corrective and preventative actions (CAPA) as required.

All serious protocol deviations/violations and serious breaches of Good Clinical Practice and/or the Trial protocol will immediately be reported to the regulatory authorities and other organisations, as required in the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended.

Accidental protocol deviations can happen at any time. They must be adequately documented on the relevant forms and reported to SCTU. Deviations from the protocol, which are found to frequently recur, are not acceptable and will require immediate action by the sponsor. Frequent non-compliances could potentially be classified as a serious breach.

Following SCTU standard operating procedures (SOPs), if the deviation is deemed a major CAPA or a potential/serious breach, the sponsor will be notified at researchsafety@uhs.nhs.uk by SCTU.

The Investigator agrees to comply with the requirements of the Protocol and Good Clinical Practice. Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used e.g. it is not acceptable to enrol a subject if they do not meet the eligibility criteria or restrictions specified in the trial protocol.

Deviations will be documented in reports to Trial Management Group ahead of meetings of this group. A copy of the TMG report with deviations can be shared with sponsor if requested.

13.4 TRIAL DISCONTINUATION

In consenting to the study, participants have consented to the Trial intervention, follow-up, and data collection. Participants may be discontinued from the Trial procedures at any time.

13.4.1 Reasons for Trial discontinuation

Participants may be discontinued from the Trial in the event of:

- Clinical decision, as judged by the Principal Investigator or CI
- Termination of trial by sponsor
- Participant choice

Full details of the reason for Trial discontinuation should be recorded in the eCRF and medical record.

13.5 WITHDRAWAL

The participant is free to withdraw consent from the trial at any time without providing a reason.

Investigators should explain to patients the value of remaining in trial follow-up and allowing this data to be used for trial purposes. Where possible, patients who have withdrawn from Trial treatment should remain in follow-up as per the trial schedule. If patients additionally withdraw consent for this, they should revert to standard clinical care as deemed by the responsible clinician. Participants should be given the option to remain in the trial for qualitative interviews, even if they withdraw consent for all other follow-up. It would remain useful for the Trial team to continue to collect standard follow-up data and unless the patient explicitly states otherwise, follow-up data will continue to be collected.

Details of trial discontinuation (date, reason if known) should be recorded in the eCRF and medical record.

13.6 PROHIBITED AND RESTRICTED THERAPIES DURING THE TRIAL

None.

13.7 BLINDING AND PROCEDURES FOR EMERGENCY UNBLINDING

The trial is not blinded.

14 SAFETY

14.1 DEFINITIONS

Adverse Event (AE): any untoward medical occurrence in a participant or clinical Trial participant which does not necessarily have a causal relationship with Trial treatment or participation.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the Trial treatment or participation (regardless of causality assessments).

Serious Adverse Event (SAE)is any untoward medical occurrence or effect that:

- **Results in death**
- **Is life-threatening** – *refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*
- **Requires hospitalisation, or prolongation of existing hospitalisation***
- **Results in persistent or significant disability or incapacity**
- Other important medical events**.

*Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.
**Other important medical events may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.
Note: It is the responsibility of the PI or delegate to grade an event as 'not serious' (AE) or 'serious' (SAE).

14.2 SERIOUSNESS

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

All adverse events that fulfil the criteria definition of 'serious' in protocol section 14.1, 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.

All SAEs must be reported immediately by the PI at the participating centre to the SCTU.

14.2.1 Exceptions:

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

- SAEs occurring prior to randomisation that are not considered to be related to trial procedures.

14.3 CAUSALITY

A complete assessment of the causality must always be assessed by a medically qualified nurse/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 the 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 applicable Research Ethics Committee will be informed of both parties' points of view.

Relationship	Denoted
Related - There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	Related and expected SAE/Related and unexpected SAE
Unrelated - There is no evidence of any causal relationship	SAE

In terms of event status; **Related and expected** SAE would signify that the SAE is related to the trial treatment and is expected (according to the list of expected events listed in the protocol; see section 14.4.1). **Related and unexpected SAE** would be classified as an SAE which is related to the trial treatment and is unexpected in terms of the events listed in the protocol.

14.4 EXPECTEDNESS

Expectedness assessments are made against the list of expected events below:

14.4.1 Expected Adverse Events:

Catheter-Associated Urinary Tract Infection (CAUTI)	Spasm
Blockage	Difficultly deflating the catheter balloon (inadequate or non-deflation of the balloon)
Pain/irritation	Leakage
Haematuria	

The nature or severity of should be considered when making the assessment of expectedness. If these factors are not consistent with the current information available then the AE should be recorded as 'unexpected'.

14.5 REPORTING PROCEDURES

The below adverse events should be reported on the relevant CRF from date of randomisation:

- CAUTI
- UTIs (not catheter-associated)
- Blockage
- Spasm
- Pain/irritation
- Difficulty deflating the catheter balloon (inadequate or non-deflation of the balloon)
- Leakage
- Haematuria
- Any other bladder or catheter related adverse event.

All serious adverse events, unless listed as an exception in section 14.2.1 should be reported to the SCTU via the method listed in section 14.5.1 from date of informed consent unless otherwise specified in the protocol. A flowchart will be provided to aid in the reporting procedures.

14.5.1 Reporting Details

For all reportable serious adverse events a SAE report form should be completed with as much detail as possible (including any relevant anonymised treatment forms and/or investigation reports) and faxed/emailed to SCTU immediately but at least within 24 hours of site becoming aware of the event.

SAE REPORTING CONTACT DETAILS

Please email or fax a copy of the SAE form to
SCTU within 24 hours of becoming aware of the event

Email: ctu@soton.ac.uk

FAO: Quality and Regulatory Team

For further assistance: Tel: 023 8120 4138 (Mon to Fri 09:00 – 17:00)

Additional information should be provided as soon as possible if the event has not resolved at the time of reporting.

The SAE Report Form asks for nature of event, date of onset, grade, outcome, causality (i.e. unrelated or related) and expectedness. The responsible investigator (or delegate) should assign the seriousness, causality and expectedness of the event with reference to the events listed in Section 14.4.1.

The event term should be the most appropriate medical term of concept and grades given in accordance with the NCI CTCAE v5.

A report of all trial SAEs will be provided to sponsor as specified in the contract or as requested, as per Standard Operating Procedure (SOP) at SCTU.

14.5.2 Follow Up and Post- Trial SAEs

The reporting requirement for all AEs and SAEs affecting participants applies for all events occurring up to the participant's next catheter change, following completion of the 12-month intervention/control period. If the participant withdraws from the intervention but chooses to remain in the trial for follow-up only, AEs and SAEs should be reported until the end of month 12.

All unresolved adverse events should be followed by the investigator until resolved of the end of trial criteria is met (i.e. lost to follow up, withdrawal etc.). At the last follow-up call, the researcher should instruct each participant to report any subsequent event(s) that the participant, or the participant's general practitioner, 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.

14.5.3 Non-serious AEs

All adverse events (as listed in section 14.5) should be recorded in the relevant eCRF and submitted to SCTU from date of informed consent. (Unless otherwise specified in this protocol)

14.5.4 Pre-existing Conditions

Any adverse events which occur after informed consent taken should be recorded on the AE eCRF as per safety reporting section.

14.6 SCTU RESPONSIBILITIES FOR SAFETY REPORTING TO REC

SCTU will notify the necessary competent authorities of all **Related and Unexpected** SAEs occurring during the trial within 15 days of notification.

SCTU submit all safety information to the REC in an annual progress report.

14.7 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. SCTU SOP 5063 will be followed for urgent safety measures.

15 STATISTICS AND DATA ANALYSES

15.1 METHOD OF RANDOMISATION

Patients will be randomised in a 1:1 ratio through a web-based system using a minimisation algorithm incorporating a random element. Factors used for minimisation will be gender, use of prophylactic antibiotics at baseline, number of average annual UTIs at baseline (less than 4/4 or more), location (own home/residential care), and Trust/Partnership.

15.2 SAMPLE SIZE

A sample size of 310 participants (155 per arm allowing for 10% loss to followup) will be required to detect a 25% absolute reduction in the mean rate of CAUTI in 12 months from 2 in the control arm. This mean rate is conservative, based on unpublished data and analysis of the Hampshire Health Record data giving an estimated value of between 2 and 3. 25% reduction (1 less UTI every 2 years) is the minimally important reduction that PPI feedback has indicated to be valuable. This is based on 90% power and alpha 5% (two-sided) using NQuery 4.0 calculation for Poisson rates. The Data Monitoring and Ethics Committee will monitor the assumptions behind the sample size calculation as the study progresses and report any recommendations to the TSC. The Data Monitoring and Ethics Committee may suggest an increase in the recruitment target if overdispersion is present and therefore a negative binomial model is required, or there are a greater than expected proportion of patients with zero CAUTIs, in which case a zero-inflated model may be required.. Equally a decrease in the recruitment target may be recommended if there is strong correlation between baseline factors and counts of CAUTI which effectively increases the available power in the study.

15.3 INTERIM ANALYSIS

No interim analysis is planned.

15.4 STATISTICAL ANALYSIS PLAN (SAP)

This trial will be analysed using the principles of the International Conference on Harmonisation E9 guidelines and reported according to the CONSORT guidelines. A full and detailed statistical analysis plan will be developed prior to the final analysis of the trial. The main features of which are described here. The primary outcome is a count outcome and will be analysed using a suitable distribution, either Poisson or negative binomial, controlling for minimisation factors and key covariates associated with the outcome. All patients will be analysed according to the treatment arm they were assigned to (intention to treat) unless otherwise specified. A full list of variables to be included in the model will be set out in the Statistical Analysis Plan. Results will be expressed as incident rate ratios with 95% confidence intervals.

Different Trusts/Partnerships have slightly differing “Catheter Care Bundles”, for example policy variation on frequency of prophylactic bladder washouts. Variation between sites will be addressed by randomisation at the individual level, stratifying for Trust/Partnership. We do not expect clustering in arms but will test and if necessary control for this during analysis.

There is the potential for patients to cross-over from their catheter type which was assigned at randomisation during a routine catheter change. A secondary analysis of the primary outcome which accounts for differences in the effect of the two types of catheter by controling for patient cross-over will be considered. Potential analysis techniques include (but are not limited to) a per protocol analysis, inverse probability of treatment weights, multiple imputation.

For analyses of secondary outcomes, the following applies. Continuous data will be presented as means and standard deviations and analysed using a linear regression modelling framework. If data are skewed, medians and ranges will be presented. To analyse skewed data we will attempt to find a suitable transformation to allow a linear modelling approach. If this is not possible, we will explore whether another suitable parametric distrbution fits the data. If not, a non-parametric approach, using quantile regression, will be used. Binary data will be reported in terms of odds ratios and analysed using logistic regression modelling. Count data will be summarised using incident rate ratios and analysed using Poisson or negative binomial regression modelling. A two-sided p-value of 0.05 will be used to assess significance throughout. Results will be presented with 95% confidence intervals throughout.

Adverse events (including pain and bladder spasm) and serious adverse events will be listed and summarised. The independent Data Monitoring and Ethics Committee will meet to monitor safety, efficacy and recruitment data throughout the trial and make recommendations regarding the continuation of the trial to the Trial Steering Committee.

Cost effectiveness

A cost effectiveness analysis will be undertaken from the perspective of the NHS. A complete record (case report form, CRF) of catheter-related activities, complications and treatments will be constructed for each participant over the 12-month intervention period by research nurses at each local recruitment site. The record will include face-to-face and telephone contacts and cover: all catheter supplies (catheters, creams, bags, valves etc.); dates of catheter changes, with reasons (e.g. planned vs. blockage etc.), location (e.g. home vs. A&E), and health professional; adverse events (e.g. infections, accidental dislodgements, leakage) with care provided, and setting; any ongoing management such as prophylactic antibiotics. The CRF will be kept up-to-date on a quarterly basis with data drawn from community nurse and nursing home records. GP databases will be accessed once at the end of the intervention period to provide information on GP and hospital service use and the prescribing of catheter supplies. The costs for each trial arm will comprise the cost of all catheter related service use, including consumables related to the catheter. Costs for the catheter supplies will be sourced from British National Formulary. Other catheter related service use will have unit costs applied using the most up-to-date versions of validated national tariffs[14,15], at the patient level for each follow up period. Costs will be aggregated over time by patient to support comparisons between groups in average costs.

The primary health-related outcome for the economic analysis will be EQ-5D-5L, completed by participants at baseline and at 3, 6, 9 and 12-month follow up points. EQ-5D-5L responses will be used to estimate the patients' health related quality of life (utility level) at each time point. This will be done by scoring the EQ-5D using a validated national tariff[16]. The utility scores will be integrated over time to provide the Quality Adjusted Life Years (QALYs), accrued by each participant over the duration of the trial.

A comparison of the difference in costs and difference in QALYs over the trial period will be conducted using appropriate statistical tests to assess significance, as outlined in statistical analysis. A cost-effectiveness analysis will be conducted to assess which treatment is most likely to be cost-effective at a given willingness to pay threshold. The cost per QALY gained (difference in cost / difference in QALYs) during the 12-month trial period will be calculated. This ICER (Incremental Cost Effectiveness Ratio), is deemed cost-effective if it falls below the NICE threshold of £20,000 per QALY[17]. This result will provide an indication of whether this treatment is cost-effective when compared to usual care (Foley). Uncertainty will be characterised based on the results of non-parametric bootstrap resampling with replacement, where for each resample of the data, the treatment with the highest NMB (Net Monetary Benefit) will be calculated [18]. Results will be presented using a cost-effectiveness acceptability curve (CEAC). The NMB changes depending how much a QALY is

valued in monetary terms. NICE suggest £20,000-£30,000 per QALY, so a range of £0 - £50,000 will be used when constructing the CEAC will show the probability that each treatment is cost-effective at a range of WTP thresholds.

The EQ-5D-5L, which is a generic measure of health-related quality of life, may not be sufficiently sensitive to fully capture the changes in health related quality of life with respects to alternative catheters. For this reason, the results will also be presented in terms of cost per unit therapeutic gain, using the catheter quality of life and differences in the number of UTIs.

16 REGULATORY

16.1 CLINICAL TRIAL AUTHORISATION

This trial is not considered to be a clinical trial of a medicinal product or medical device, so clinical trial authorisation from the UK Competent Authority the Medicines and Healthcare products Regulatory Agency (MHRA) is not applicable.

17 ETHICAL CONSIDERATIONS

The trial will be conducted in accordance with the recommendations for physicians involved in research on human participants adopted by the 18th World Medical Assembly, Helsinki 1964 as revised 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 study, the clinician may give alternative treatment to that specified in the protocol, 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 protocol treatment and trial follow-up without giving reasons and without prejudicing their further treatment.

17.1 SPECIFIC ETHICAL CONSIDERATIONS

Clinical data will be captured using the iMedidata RAVE database platform, which is hosted on servers based in the United States of America. However, the Medidata team will not have access to the trial data and no data will be sent outside the UK.

17.2 ETHICAL APPROVAL

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

The sponsor will ensure that the trial protocol, patient information sheet, consent form, GP letter and submitted supporting documents have been approved by the appropriate regulatory body, Health Research Authority (HRA), main research ethics committee (REC) and that local permission has been obtained prior to any subject recruitment.

All substantial amendments and non-substantial amendments (as determined by the sponsor) will not be implemented until HRA/REC have provided the relevant authorisations. The NHS R&D departments will also be informed of any substantial amendments and non-substantial amendments. Relevant approvals must be obtained before any substantial amendment and non-substantial amendments may be implemented at sites.

All correspondence with the HRA and the REC will be retained in the Trial Master File and the Investigator Site File (maintained by the site).

An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended.

Within 90 days after the end of the trial (as defined in section 7.10), the CI/Sponsor will ensure that the HRA and the main REC are notified that the trial has finished. If the trial is terminated prematurely, those reports will be made within 15 days after the end of the trial.

The CI will supply the Sponsor with a summary report of the clinical trial, which will then be submitted to the main REC within 1 year after the end of the trial.

All results will be published on a publicly accessible database.

17.3 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 patient information leaflet. 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.

17.4 CONFIDENTIALITY

SCTU will preserve the confidentiality of participants taking part in the study, in accordance with GDPR and data protection complaint. The investigator must ensure that participants' anonymity will be maintained and that their identities are protected from unauthorised parties. On e/CRFs participants will not be identified by their names, but by an identification code.

18 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 study) are detailed in the Non-Commercial Agreement.

18.1 INDEMNITY

For NHS sponsored research HSG (96) 48 reference no.2 applies. If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS Indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the study. NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim.

18.2 FUNDING

This Trial is funded by the NIHR Health Technology Assessment Programme.

18.2.1 Site payments

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

This trial is automatically eligible for the NIHR portfolio. This enables Trusts to apply to their comprehensive local research network for service support costs, if required.

18.2.2 Participant payments

Participants will not be paid for participation in the main trial. Interview participants will receive a £15 gift voucher.

18.3 AUDITS AND INSPECTIONS

The trial may be participant to inspection and audit by University Hospital Southampton NHS Foundation Trust (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.

19 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, the Trial Steering Committee and the Data Monitoring and Ethics Committee.

19.1 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 CaDeT 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.

19.2 TRIAL STEERING COMMITTEE (TSC)

The TSC act as the oversight body on behalf of the Sponsor and Funder. The TSC will meet in person at least yearly and have at least one further teleconference meeting during the year. The majority of members of the TSC, including the Chair, should be independent of the trial.

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

19.3 INDEPENDENT DATA MONITORING COMMITTEE (IDMC) /DATA MONITORING AND ETHICS COMMITTEE (DMEC)

*(**NB** for the purposes of this protocol, IDMC and DMEC refer to the same committee, and these terms can be used interchangeably).*

The aim of the IDMC is to safeguard the interests of trial participants, monitor the main outcome measures including safety and efficacy, and monitor the overall conduct of the study.

The CaDeT DMEC charter defines the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the IDMC, including the timing of meetings, methods of providing information to and from the IDMC, frequency and format of meetings, statistical issues and relationships with other trial committees.

20 DATA MANAGEMENT

Participant data will be entered remotely at site or by recruitment hubs in electronic case report forms and retained in accordance with the current Data Protection Regulations. The PI is 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 eCRFs. When requested, laboratory data must be transcribed, with all investigator observations entered into the eCRF. 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.

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

20.1 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.

21 MONITORING

21.1 CENTRAL MONITORING

Data stored at SCTU will be checked for missing or unusual values (range checks) and checked for consistency within participants over time. Any suspect data will be returned to the site in the form of data queries. Data query forms will be produced at SCTU from the trial database and sent either electronically or through the post to a named individual (as listed on the site delegation log). Sites will respond the queries providing an explanation/resolution to the discrepancies and return the data query forms to SCTU. The forms will then be filed along with the appropriate CRFs and the appropriate corrections made on the database. 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.

The DMEC also have responsibility for specific central monitoring activities.

21.2 CLINICAL SITE MONITORING

Given the nature of the trial, Site monitoring is not expected. Monitoring visits may be triggered if there are concerns with a site.

On receipt of a written 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). Access should also be given to study staff and departments.

The participants' medical records and other relevant data may also be reviewed by appropriate qualified personnel independent from the SCTU appointed to audit the study, including representatives of the Competent Authority. Details will remain confidential and participants' names will not be recorded outside the study site.

21.2.1 Source Data Verification

On receipt of a written 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). Access should also be given to trial staff and departments.

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

21.3 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.

22 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. All source documents will be retained for a period 25 years following the end of the trial.

Sites are responsible for archiving the ISF and participants' medical records.

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

23 PUBLICATION POLICY

Data from all centres will be analysed together and published as soon as possible in peer-reviewed journals.

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.

All publications arising from this work will acknowledge the organisations involved in the research - University of Southampton and University Hospital Southampton NHS Foundation Trust. The policy applies to all staff and students whose research outputs from pre-clinical and clinical research derive from their employment by the University and/or Trust, from research grants awarded to the University and/or Trust or otherwise from the use of University and/or Trust resources and facilities. The policy applies to all authors of publications, and not simply to principal authors or reprint authors. Citing both organisations on all papers covered by this policy acknowledges the success of each organisation resulting from working in partnership.

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25 APPENDIX 1 – CATHETER FIGURES

Figure 1. Standard 'Foley' Catheter

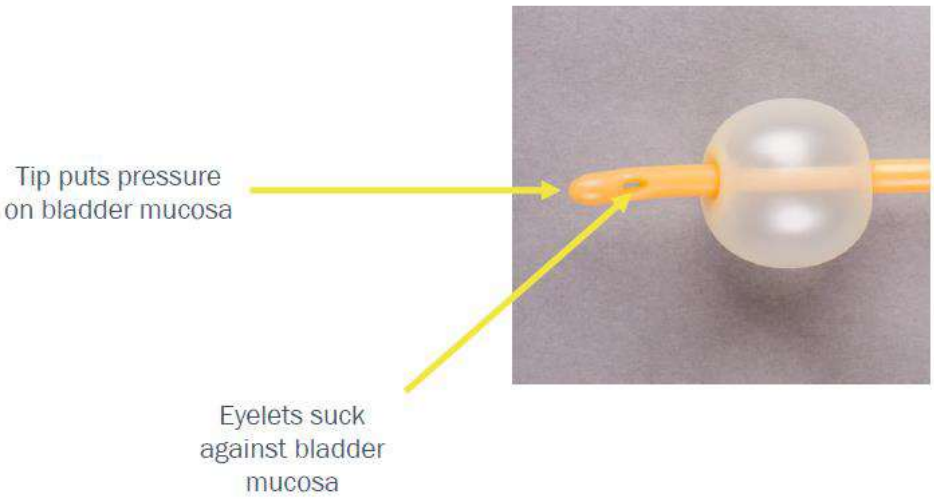
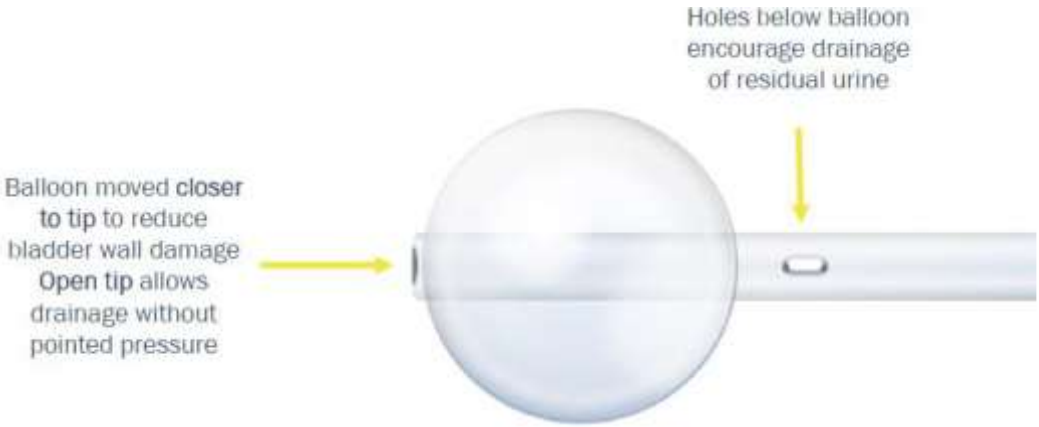


Figure 2. Optitip Catheter



SUMMARY OF SIGNIFICANT CHANGES TO THE PROTOCOL

Protocol date and version	Summary of significant changes
V1 18-Jul-2022	Original document.
V2 19-Jan-2023	• Addition of funder statement on page 3 • Addition of trial duration on page 10 • Claire Forbes removed as Trial Manager • Addition of URL for RAVE database and randomisation system • Collection of employment status in baseline CRF (page 21) was missed in protocol v1 18-Jul-2022 • Clarification how contact details will be added to eConsent platform (page 22) • Removal of phrasing that patient should be advised not to reveal catheter allocation during follow-up calls (page 23) • Clarification that qualitative interview with patients allocated to the Optitip arm would be conducted from Month 9 onwards or at point of patient withdrawal when patient ceases trial participation • Details for arrangements for continued provision of intervention catheter after trial participation has ended
V3 27 Sep 2023	• Susanne Renz removed as Trial Manager, page 2 • Alannah Morgan added as Trial Manager, page 2 • Dr Beth Stuart removed as Co-investigator, page 2 • Dr Sam Wilding added as Co-investigator, page 2 • A change in title for Co-investigator Andrew Cook, from Dr to Professor • A change to process, clinical care team or the research team to make one attempt to contact non-responders to the invite by telephone (with a pre text), within a minimum of 3 weeks of sending out the invitation to the patient, section 12.1.1 • Addition of the reminder invite letter, update to the protocol was missed when the implementation of this document was approved, section 12.1.1 • Use of social media and recruitment poster, to raise awareness of cadet in the patient and nursing community, section 12.1.1 • Methods to improve patient retention by reducing the patient burden of telephone calls and postal returns, section 13.2.1
V4 11 Jan 2024	• Update to Table 1 (Trial Synopsis) to include the secondary endpoints for the qualitative interviews with patients that decline to take part in cadet. • Update to Table 5 (Trial Objectives) to include qualitative interviews with patients that decline to take part in cadet. • Update to section 6.1.3, to include qualitative interviews with patients that have declined to take part in cadet. • A statement added to section 12.1.1, to include qualitative interviews with patients that decline to take part in cadet. • Update to section 13.2.6 to include the number of participants to be approached for the qualitative interviews: 15 trial participants, up to

	2 healthcare professionals from each community trust, and 15 patients who declined the trial.