URINARY CATHETER ‘FILL AND FLUSH’ VALVE:

SAFETY, EFFECTIVENESS, ACCEPTABILITY AND FEASIBILITY TRIAL

URINARY CATHETER VALVE STUDY

Sponsor Study reference: ERGO 41448

IRAS: 245818

Protocol version: 3.1
Date: 20/08/2019

Chief Investigator: Professor M. Fader

AMENDMENT HISTORY

Amendment No.	CIP Version No.	Date Issued	Author(s) of Changes	Details of Changes
1	2.0	30/11/2018	Dr. Catherine, Murphy, Jade Rand	• Updated sponsor reference number and additional contact details added for protocol signatories and sponsor representative. • Page numbers and sub titles added. • Anticipated timelines for trial have been updated. • Site numbers and recruitment methods clarified. • Reference to planned later phase trials using the device have been removed. • Corrections made to information on research site. • Participant visits and sample groups clarified. Full list of study procedures for Day 2 added. Visit flow charts put into appendices. • More information provided on data handling and record keeping. • Safety reporting methods have been clarified. • End of clinical investigation defined as 2 weeks after last participants' last visit (LPLV).
2	2.1	07/12/2018	Dr. Catherine, Murphy, Jade Rand	• Manufacturer clarified. • Recruitment via Southern Counties Continence Forum removed. • Recruitment via GP surgeries as participant identification centres (PICs) clarified. • Fluid provisions on visit days confirmed. • More information provided on data analysis. • Safety stopping criteria added. • Reference to SOP-RES-017 removed. • Layout of protocol amended.
3	3.0	29/01/2019	Dr. Catherine, Murphy, Jade Rand	• Statement of compliance corrected from 'Research Governance Framework' to 'UK Policy Framework for Health and Social Care Research'. Reference to applicable device regulations added. • References to electronic database changed to read study

				database (excel spreadsheet). • Eligibility criteria amended to include requirement to drink 500mls in the first 2 hours of the intervention period. • Clinically significant adverse events that would be considered stopping criteria have been added. • Stopping criteria amended to reflect safety cohort in group 1. • Ethnicity data will no longer be collected. • Further information provided on study design regarding safety cohort in Group 1. • Layout of protocol amended. • Abbreviations list updated. • Safety reporting procedure clarified. • Anticipated study timelines adjusted. • Valve fitting and reconciliation clarified. • Reference to trial monitoring plan added,
4	**3.1**	**20/08/2019**	Dr. Catherine, Murphy, Jade Rand	• Anticipated timelines for trial have been updated. • Sponsor representative details updated. • Page numbering corrected.

Statement of Compliance

This clinical investigation will be conducted in compliance with the Clinical Investigation Plan (CIP) and applicable regulatory requirements; adhering to UK Policy Framework for Health and Social Care Research and the Medical Devices Regulations 2002 (SI 618), as amended by the Medical Devices (Amendment) Regulations 2008 (SI 2936).

This Clinical Investigation Plan (CIP) describes the clinical investigation and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators within the clinical investigation. Problems relating to this clinical investigation should be referred, in the first instance, to the Chief Investigator.

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Sponsor

University of Southampton is the research sponsor for this clinical investigation. For further information regarding the sponsorship conditions, please contact:

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Funder

NIHR i4i
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Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host NHS Trust(s), regulatory authorities, and members of the Research Ethics Committee.

Investigator Agreement

"I have read this protocol and agree to abide by all provisions set forth therein.
I agree to comply with the principles of the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice."

Professor M. Fader ……..…… ……..
Chief Investigator *Investigator Signature* *Date*

Conflict of Interest

1. "According to the Declaration of Helsinki, 2008, I have read this protocol, and declare no/the following (delete as appropriate) conflict of interest"

Professor M. Fader ……..…… ……..
Chief Investigator *Investigator Signature* *Date*

2. "According to the Declaration of Helsinki, 2008, I have read this protocol, and declare no/the following (delete as appropriate) conflict of interest"

Dr C. Murphy ……..…… ……..
Principal Investigator *Investigator Signature* *Date*

Contents

1. ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
CIB	Clinical Investigator Brochure
CIP	Clinical Investigation Plan
CRF	Case Report Form/ Clinical Research Facility
GCP	Good Clinical Practise
GP	General Practitioner
ICF	Informed Consent Form
ICH	International Conference of Harmonisation
MHRA	Medicinal Health Research Authority
NHS	National Health Service
NRES	National Research Ethics Service
PI	Principle Investigator
PIL	Participant Information Sheet
R&I	Research & Innovation
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
UHS	University Hospital Southampton
USADE	Unanticipated Serious Adverse Device Effect

2. CLINICAL INVESTIGATION SUMMARY

Clinical Investigation Title	URINARY CATHETER 'FILL AND FLUSH' VALVE: SAFETY, EFFECTIVENESS, ACCEPTABILITY AND FEASIBILITY TRIAL
Sponsor Reference Number	41448
Trial Centre(s)	NIHR Clinical Research Facility, Southampton University Hospital NHS Foundation Trust, Southampton, SO16 6YD
Clinical investigation Design	'First in human' Safety and acceptability testing
Population	Long-term indwelling urinary catheter (IDC) users
Sample Size	16
Planned Clinical investigation Period	Six months
Primary Objective	To assess preliminary safety, effectiveness, reliability, comfort and user acceptability of the device with adults who have a long-term IDC.
Primary End points	Evaluation of the effectiveness of bladder drainage (Valve Log)
Secondary End points	Patient reported outcome measures (EQ-5D, Long-term catheter Quality of Life Questionnaire, Valve log)
Device Name	Fill and Flush Valve (the 'valve')
Manufacturer Name	Rainbow Medical Engineering Ltd
Principle Intended Use	To facilitate the automatic filling and flushing of the bladder when a urinary catheter is in situ.
Anticipated Timelines	Commence recruitment – *September 2019* Commence data collection – *October 2019* Complete data collection – *December 2020* Complete data analysis – *February 2020* Issue pilot phase report – *March 2020* These timelines are subject to change and are dependent on securing all required approvals.

3. INTRODUCTION

3.1 Background to the study

Indwelling urinary catheters (IDC) are a medical device designed to aid bladder drainage. They are used by male and female in-patients and community-dwellers (residential/nursing homes and private homes) of all ages. They may be temporary e.g. post operatively or following trauma for accurate measurement of urine output , or long-term / permanent for those with voiding dysfunction or incontinence not amenable to treatment or alternative forms of management. IDCs comprise a pliable, hollow tube (20-40cm for women or men respectively) usually made from latex or silicone with drainage eyes at the proximal end, a drainage channel or lumen and a connecting funnel at the distal end.

They may be 'urethral' when inserted via the urethra or 'supra-pubic' when inserted via a small tract just above the pubis; in both cases the IDC is secured in place with a balloon filled with sterile water which is inflated after insertion. They are connected to a drainage bag and/or a manual catheter valve (with or without a drainage bag attached to the valve) to allow continual drainage or periodic emptying respectively.

Over 12% of NHS patients have an IDC (1) and they can be useful devices but are commonly associated with complications such as catheter-associated urinary tract infection (CAUTI). Importantly, they are the second most common cause of nosocomial (hospital acquired) infection, leading to 2,100 deaths per annum in the UK, 225,000 infections and healthcare costs of an estimated £1billion (2). For the 90,000 long-term IDC users in the UK, device blockage is one of the most frequent and costly complications (3) and is caused by the colonisation of the catheter by urease producing bacteria leading to extensive biofilm and crystallisation (4). Blockages have the potential to lead to pyelonephritis, septicaemia and endotoxic shock (4) and cause considerable pain and distress to patients (5). A recent study of long-term catheter use in England found that 40% of patient's devices blocked at least once every three months, with 20% blocking up to three times per month (Avery et al forthcoming). The need to manage blockages rapidly requires high NHS community resource-use and is the most frequent cause of unplanned catheter care (6,7). Interventions, including the use of novel catheter materials, bacteriophage therapy, catheter maintenance solutions or behavioural modifications, have yet to reduce blockage in clinical practice.

The flow of urine through IDCs can be managed by free drainage (with an attached urine collection bag) or by the filling and emptying of the bladder using a catheter valve (generally with no urine collection bag). Catheter valves are used with IDCs in isolation or in combination with a urine drainage bag. They are typically connected at the proximal end to the IDC by insertion into the funnel end of the catheter. At the distal end they are connected to the drainage bag in a similar way. The purpose of a catheter valve is to allow the bladder to fill and empty periodically thus mimicking normal bladder physiology. A theoretical model has been proposed whereby free drainage of urine into a drainage bag promotes the development of biofilm, crystallisation and subsequent blockage, whereas the mechanism of repeatedly filling and emptying produced with the use of a valve reduces blockage. This theory has been demonstrated to be valid in laboratory models with valve regulated urine flow increasing time to blockage compared to free drainage (mean 62.6 vs 35.9 hours, $p = 0.039$) (8). Additionally, there is evidence that bladder filling and voiding is important in maintaining bladder health by limiting local inflammatory responses in long-term IUC users (9).

Current catheter valves are 'manual' and require the user to open the valve either routinely or in response to an 'urge to void'. Therefore a) the user must have sufficient cognitive skills to ensure safe use of the device i.e. not to allow the bladder to overfill which, long-term, can damage the upper urinary tract and b) the valve may be opened and the bladder emptied before optimum bladder filling has occurred which over time may lead to reduced bladder capacity. Manual catheter valves are used by around 18% of the long-term IDC population.

3.2 The 'fill and flush' valve:

The fill and flush valve (Figure 1) is an automated valve which is designed to open in response to rising bladder pressure which occurs as the bladder becomes full. The valve is situated between the IDC and the drainage bag as a manual valve would be.

A detailed description of the valve is provided in the Clinical Investigator Brochure (CIB). Manufacturer's Part Numbers are as follows:

- EM02 Low Pressure Release
- EM03 Medium Pressure Release
- EM04 High Pressure Release

There are three variants of the valve which respond to different degrees of bladder pressure. People's bladders function at different pressure levels. One of the aims of this study is to gain preliminary data on which valve variant works and under which circumstances. Pressure ranges are as follows:

Low: 22 - 49cm H_2O

Medium: 35 - 61cm H_2O

High: 53 - 79cm H_2O

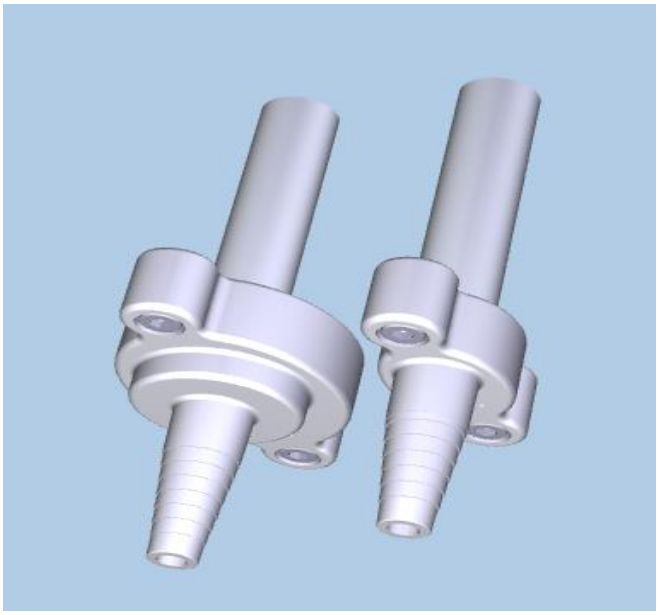


Figure 1 Fill and Flush Valve

This valve is not currently CE marked and therefore an application has been made to the Medicines and Healthcare products Regulatory Agency (MHRA) for a Notice of No Objection to use it in this research study. The valve has shown promise for bladder drainage in preliminary laboratory studies using an experimental urinary tract (see section 3.5).

3.3 Intended Purpose and proof of concept:

It is intended that the automated valve will open, allowing urine to drain from the bladder in response to rising bladder pressure without the user needing the dexterity to open a manual valve. The intended population are long-term catheter users who are unable to use a manual valve but want the anticipated benefits of a 'fill and flush' mechanism. The valve will attach to the external end of the catheter, with a drainage bag attached to the other end of the valve.

3.4 Risks and Benefits

It is hypothesised that the benefit of the valve is this could overcome the problems cited above by ensuring optimal bladder filling followed by swift urine drainage and flushing of the catheter and drainage bag lumen thereby also reducing the risk of biofilm formation and blockage.

The potential risk is that the valve will not open or will not fully drain the bladder. This risk will be mitigated by only recruiting participants who have bladder sensation and who can report any discomfort, by scanning the bladder hourly to check the volume of urine has not risen above acceptable levels and by removing the valve should any problems occur.

3.5 Laboratory testing:

The valve has undergone laboratory testing at the Bristol Urological Institute which show that a simple valve allowing the bladder to naturally 'fill and flush' stops bacteria for more than fourteen days. Glass bladder models were used to evaluate the performance of the valve in situ to demonstrate functionality when compared with free drainage as follows:

1. Catheters were inserted into glass bladder models and set up with the valve housing inserted between the catheter and drainage bag in both models. One model had no valve (Control) and one had a blue valve inserted (Test).
2. Both models were supplied with artificial urine.
3. 30mls of an overnight culture of a clinical strain of *Proteus mirabilis* was pipetted into the drainage tube between the connection with the valve housing and left for 1 hour with no urine flow to allow the bacteria to become established.
4. The urine flow was switched on at a rate of 1ml/min and the models allowed to run until *Pr. mirabilis* was detected in the glass bladder. This was done by removing 5ml of urine from the bladder every 24hrs. pH and viable bacterial numbers were recorded.
5. The time for *Pr. mirabilis* to migrate to the bladder was recorded for the Control and Test models.
6. These experiments were repeated in triplicate.

The study has demonstrated that the valve reliably opened and closed periodically for up to 14 days and prevented the migration of *Pr. mirabilis* up through the drainage system to the bladder when compared to a non-valved continuous drainage model. *Pr. mirabilis* was not detected in any of the valved models (Table 1.).

Table 1 – Summary of times taken for *Pr. mirabilis* to migrate up to the bladder in Control and Test Models.

Run 1		Run 2		Run 3	
Control	Test	Control	Test	Control	Test
>120 h	>120 h	144 h	>288 h	168 h	>336 h

4. CLINICAL INVESTIGATION OBJECTIVES

The next stage is for the prototype valve to be tested clinically in humans under research conditions; this will establish if the device reliably opens and closes and is safe to use.

4.1 Research Questions:

1. Does the valve function reliably and effectively?
2. Does the valve provide a safe method of emptying the bladder?
3. Does the valve provide a method of emptying the bladder which is acceptable to users e.g. for comfort?
4. Is a community-based trial of the valve feasible and desirable?

4.2 Objectives

To assess preliminary safety, effectiveness, reliability, comfort and user acceptability of the valve with adults who have a long-term IDC and the feasibility of undertaking future community-based evaluation.

To do this we will:

- determine if the valve functions reliably i.e. automatically opens to drain urine within acceptable individual bladder volumes with a range of patients;
- determine if the valve functions effectively i.e. allows for the complete bladder emptying (< 100ml post void residual) during rest and daily activities;
- determine if the process of filling and automatic draining is comfortable and acceptable for participants;
- collect preliminary data on the potential for bioburden/biofilm following in human use of the valve;
- assess the feasibility of undertaking a future randomised control trial of the valve.

4.3 Outcomes

4.3.1 Primary outcomes:

Safety: Reliability

- Valve opening - Proportion of observations of automatic valve opening before bladder capacity (500ml or less) is reached - as measured by bladder scanner (Valve Log)

Safety: Effectiveness

- Bladder emptying - proportion of valve voids with residual urine <100ml – as measured by bladder scanner (Valve Log)
- Participant report (Valve self-report questionnaire)

Comfort

- Participant report (Valve self-report questionnaire)

4.3.2 Secondary outcomes:

User acceptability

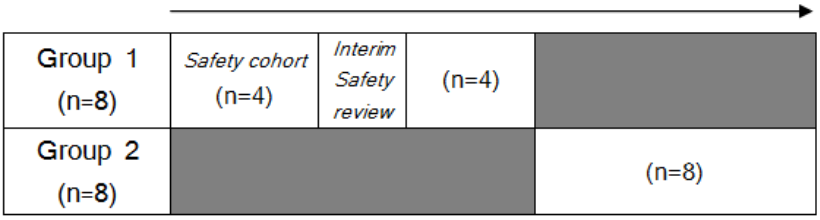
- Valve self-report questionnaire (Valve self-report questionnaire)

Quality of life

- EQ-5D-5L and Long-term Catheter Quality of Life Tool

5. CLINICAL INVESTIGATION DESIGN

This study a 'first in human' assessment of reliability, effectiveness, comfort and user acceptability with 16 long-term catheter users.
This study will be in one phase over 6 months, and compromise of 2 groups:



Group 1- The valve will initially be tested in 8 participants who currently use a standard manual valve (without leg-bag). Such participants (and their bladders) will be accustomed to the filling and emptying of the bladder with an IDC in situ and therefore represent the most predictable and safest population on which to test the valve.

This first group will include a safety cohort of participants (n=4). All safety data will be reviewed from the initial 4 participants before further participants can undergo the study investigation. Review of the initial data will include an interim safety report submission to the Medicines and Healthcare products Regulatory Agency (MHRA) in line with the issued Notice of No Objection.

Once all relevant permissions to proceed have been granted, the valve will then be tested in the remainder of standard manual valve participants (n=4) to complete Group 1.

Group 2 - The valve will then be tested with participants (n=8) who currently use a drainage bag with free drainage in order to test the valve with people who are no longer accustomed to the process of filling and emptying the bladder (Group 2).

After use (in both groups), the valves will be examined microbiologically in the University of Southampton laboratory to detect bioburden and/or biofilm to ascertain a baseline for future studies.

5.1 Setting:

This 'first in human' phase will take place in controlled conditions at the Southampton NIHR Clinical Research Facility (CRF) at University Hospital Southampton NHS Foundation Trust.

Some of the key safety measures in place include:

- The Southampton NIHR Clinical Research Facility (CRF) is located within University Hospital NHS Foundation Trust, adjacent to the acute medical and intensive care wards.
- Clinical nursing staff based in the NIHR CRF are Immediate Life Support (ILS) trained (with annual updates) as a minimum.

- Clinical staff based in the CRF attend an emergency scenario training session at least annually.
- Standard Operating Procedures (SOPs) are in place for managing common medical emergencies such as anaphylaxis, syncope etc.
- Emergency resuscitation trolleys are in place throughout the facility.
- Emergency call bells are tested every three months to ensure that they are in working order, and a bi-weekly check of pull cords is conducted to make sure they are accessible and have not been tied up or moved out of reach.
- As a hospital ward, the NIHR CRF has full use of the 24 hour emergency response teams in case of a medical emergency.
- A hospital style bed will be provided.

Each participant will attend two visits (up to a maximum of 7 hours per day) at the CRF testing the valve.

Appropriate refreshments will be provided, and travel expenses will be reimbursed.

5.2 Equipment:

5.2.1 Trial Valves:

The trial valves will be provided sterile by the manufacturer Rainbow Medical Engineering Ltd. The valves and packaging will be labelled for clinical trial only with additional information as set out in the CIB. Three valves (one of each pressure variant) will be provided for each participant per day, plus 8 additional spare devices (= total of 24 per variant).

Each valve will be identified with a unique serial number, batch number and patient label set. All reference numbers will be recorded against participant study IDs on a reconciliation log.

Study teams will be trained on changing and/ or replacing trial valves as per study specific SOP.

5.2.2 Standard valves:

Each participant will be given a new valve of the type they usually use after testing is complete on each day. Therefore 16 standard (manual) valves will be required.

5.2.3 Drainage bags:

One drainage bag will be provided at the start of each day/testing period (16 in total).

5.2.4 Bladder scanner:

A new scanner will be purchased for study use.

5.2.5 Absorbent pads:

To protect participant's clothing from any leakage. One pad per participant visit (n=32)

5.3 Sample:

Sixteen men and women aged 18 or over who have a long-term indwelling urinary catheter in situ (urethral or suprapubic) and use either a manual valve or a drainage bag. Sixteen is anticipated to be a sufficient sample size to address the preliminary 'first in human' research questions on effectiveness, usability and acceptability.

5.4 Recruitment and consent:

We will recruit 16 long-term IDC users (8 who currently use a standard manual valve e.g. a 'flip-flo' – with or without an attached drainage bag- and 8 who use just a drainage bag).

5.4.1 Recruitment Methods

Local GP practices will be invited to act as Participant Identification Centres (PIC) sites. This will supported by Wessex Clinical Research Network:

- PIC sites will be asked to search for long-term catheter users (including those who use valves and drainage bags or drainage bags only) and asked to identify potential participants using the eligibility criteria.
- PIC sites will then provide or send a letter of invitation containing an expression of interest form with a freepost return envelope to prospective participants.
- PIC sites will be provided with a flyer that includes a brief description of the study and contact details for the research team. This can to be provided to urinary catheter users or used as a poster.

If full recruitment numbers have not been achieved in the anticipated timelines:

- Local NHS sites may also be invited to act as Participant Identification Centres (PIC). All relevant sponsor, ethical and regulatory approvals will be sort prior to implementing this change.

5.4.2 Patient Information Sheets

In each case, the potential recruits will be asked to contact the research team directly (providing their contact details) if they wish to find out more about the study. Potential participants will be sent a Participant Information Sheet (PIS). This will be followed up (no sooner than 24 hours after they have received the PIS) with a phone call to discuss the study, answer any questions and check eligibility.

5.4.3 Confirmation from General Practitioner

Those who wish to participate, who have not been identified by their GP, will then be sent a form to obtain their written consent for the research team to contact their GP for a letter of confirmation of health status and potential eligibility to participate in study.

5.4.4 Informed Consent Process

Participants will be required to give informed consent at the first visit to the Clinical Research Facility. The person who obtains the consent must be suitably qualified and experienced, check eligibility, and have been authorised to do so by the Chief/Principal Investigator.

The participant must personally sign and date the latest approved version of the informed consent form before any clinical investigation specific procedures are performed. It will be clearly stated that the participant is free to withdraw from the clinical investigation at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

A copy of the signed Informed Consent will be given to the participants. The original signed form will be retained at the clinical investigation site.

5.5 Eligibility criteria

5.5.1 Inclusion criteria

- IDC-users (urethral or suprapubic), over 18, who have had a catheter in situ for at least one month and use a manual valve or drainage bag to collect urine
- Independent with catheter care needs (e.g. bag emptying or valve opening)
- Able to transfer from bed to chair, stand and walk short distances unaided
- Able to drink moderate levels of fluid (500mls in the first 2 hours and 150mls per hour thereafter)
- Able to provide informed consent (self-report and research nurse assessment)
- Usual medical provider provides confirmation of suitability

5.5.2 Exclusion criteria

- End stages of a terminal illness
- Current treatment of urinary tract infection
- Has been advised by a urologist against using a valve on clinical grounds
- Lack of bladder sensation (e.g. unable to sense when bladder needs emptying)
- Previous bladder surgery that could affect the integrity of the bladder
- At known risk of autonomic dysreflexia

5.6 Trial Procedures & Data Collection

There will be 2 groups of participants and the data collection process will be identical for both groups. Participants in both groups will undergo the following procedures (detailed in Flow charts in Appendix B and C):

5.6.1 Trial Procedures: Day 1 – Non-ambulatory testing

Pre-testing

- Confirm eligibility, answer any questions and ask participant to confirm consent (recorded on Day 1 Case report form).
- First drink (250mls) provided.
- Record demographic data on Day 1 Case report form (date of birth, address, telephone number, GP address).
- Take baseline observations and record on Day 1 Case report form: blood pressure, temperature, pulse and respiratory rate.
- Participant completes Quality of Life tools: EQ-5D-5L and Long-term Catheter Quality of Life Tool.

Testing Procedure

With the participant sitting (except when transferring to and lying on the bed for bladder scanning):

1. Participant puts on pad with pants to secure it in place
2. Record participant's self-reported bladder sensations
3. Scan bladder and record volume in Valve Log.
4. Research nurse fits the lowest pressure valve according to manufacturer's instructions for use and attach a drainage bag for urine collection. Record Valve Batch/Serial Number in Valve Log.
5. Record participant's self-reported bladder sensations in valve log
6. Scan bladder and record volume in valve log
7. If the valve remains open with urine draining freely, replace with the next level pressure valve (up to 3 valves) until free drainage has ceased and the valve remains closed. Record Valve Batch/Serial Number in Valve Log.

8. Participant to lie on bed for hourly bladder scanning (record time and volume in Valve Log) until bladder volume is >400mls or the participant experiences bladder discomfort or the valve automatically opens. Record participant's bladder sensations before each scan and:
    a. If the volume is >400mls or the participant is experiencing discomfort
        i. Ask the participant to contract abdominal muscles, press down on abdomen or bear down as if trying to pass urine to increase bladder pressure.
        ii. If the valve opens, proceed as below (b).
        iii. If the valve does not open, disconnect the valve, attach a new drainage bag and allow the bladder to drain. Stop the trial for that participant.
    b. If the valve automatically opens:
        i. Record the amount of urine voided
        ii. Scan the bladder for any residual volume
9. If the valve has opened with a urine volume of less than 500ml, repeat process 7 & 8 at 1 hourly intervals for 5 hours. If the valve did not open before bladder volume reached 500ml, stop testing at this point.

Participants will be requested to drink a minimum of 500mls of fluids over the first two hours, then a minimum of 150mls per hour for the next 3 hours. They will be given a choice of drinks. After testing has ended for that day, participants will be given a new manual valve and/or drainage bag as per usual use.

5.6.2 Trial Procedures Day 2 - Ambulatory testing

Pre-testing

- Confirm no changes to eligibility, answer any questions and ask participant to re-confirm consent (recorded on Day 2 Case report form).
- First drink (250mls) provided.
- Take baseline observations and record on Day 2 Case report form: blood pressure, temperature, pulse and respiratory rate.
- Participant completes Quality of Life tools: EQ-5D-5L and Long-term Catheter Quality of Life Tool.

Testing Procedure

With the participant sitting (except when transferring to and lying on the bed for bladder scanning):

10. Participant puts on pad with pants to secure it in place
11. Record participant's self-reported bladder sensations
12. Scan bladder and record volume in Valve Log
13. Participant fits the lowest pressure valve according to manufacturer's instructions for use and attach a drainage bag for urine collection.
14. Record Valve Batch/Serial Number in Valve Log.
15. Record participant's self-reported bladder sensations in valve log
16. Scan bladder and record volume in valve log
17. If the valve remains open with urine draining freely, replace with the next level pressure valve (up to 3 valves) until free drainage has ceased and the valve remains closed. Record Valve Batch/Serial Number in Valve Log.
18. Participant will be asked to stand, walk around and cough at specific intervals as per flowchart in appendix C.

19. Record participant's bladder sensations before each scan and:
    a. If the volume is >400mls or the participant is experiencing discomfort
        i. Ask the participant to contract abdominal muscles, press down on abdomen or bear down as if trying to pass urine to increase bladder pressure.
        ii. If the valve opens, proceed as below (b).
        iii. If the valve does not open, disconnect the valve, attach a new drainage bag and allow the bladder to drain. Stop the trial for that participant.
    b. If the valve automatically opens:
        i. Record the amount of urine voided
        ii. Scan the bladder for any residual volume

As with Day 1, participants will be requested to drink a minimum of 500mls of fluids over the first two hours, then a minimum of 150mls per hour for the next 3 hours. They will be given a choice of drinks. After testing has ended for that day, participants will be given a new manual valve and/or drainage bag as per usual use.

If a participant has to stop testing during Day 1 they will not be eligible for any further testing. All data will be collected by an appropriately trained research nurse (RN).

Valve Questionnaire: After all testing is completed; participants will complete a Valve Questionnaire to assess the valve for comfort.

Microbiological Testing: Used valves will be collected and placed in individual, labelled, sealed plastic bags. These will be transported to the ACDP Containment Level 2 microbiology laboratory in the Life Sciences Building, Highfield Campus, University of Southampton. Valves will be packaged as UN 3373 Biological Category B specimens for transportation. The sealed bags will be placed in secondary packaging with absorbent tissue. This will be sealed and labelled UN 3373. Samples will then be transferred to the laboratory and only opened within the Containment 2 facility.

If there is a delay between collection of used valves and transportation to the laboratory, the sealed bags will be stored in a refrigerator until collection. This will prevent additional growth of any bacteria which may be present.

All laboratory staff will be adequately trained in GCP and according to all applicable local policies and procedures.

5.7 Withdrawal:

Participants will be able to withdraw from the study at any point without giving a reason. Withdrawal will be recorded in the Case Report Form.

5.8 IDC Management after End of the study:

Once the participant has completed the study s/he will be advised to revert to his usual method of IDC management.

5.9 Data Analysis:

5.9.1 Clinical

Descriptive statistics will be used to summarise

- Demographics of participants
  - Total number and percentage of men and women will be reported
  - Total number and percentage from each age groups will be reported
- Bladder volume when the valve opened and residual bladder volume when the valve closed while undertaking different activities
  - The range and mean average of the volume of urine in the bladder at each valve opening for each activity will be reported.
- Questionnaire findings (for each occasion the questionnaire is completed)
  - For binary questions (yes/no), the total number and percentage of each answer will be recorded
  - For scale response questions, the total and percentage number of participants answering each response (e.g. Very comfortable, Quite comfortable, neither comfortable or uncomfortable, Quite uncomfortable, Very uncomfortable) will be reported.

5.9.2 Laboratory

Microbiological analysis will be carried out on the lumen of all test valves. The presence of biofilm formation will be assessed and if present analysed by direct and indirect methods. Sections will be examined directly using episcopic differential interference contrast (EDIC) microscopy, which provides information on the development and structure of biofilms and shows interaction between the bacteria and catheter material. For indirect analysis, any attached bacteria and biofilm will be mechanically removed and re-suspended. This will then be analysed by culture (as described for urinalysis) and microscopy, using viability stains to quantify viable but non-culturable bacteria (VBNC).

6. SAFETY REPORTING

The definitions of adverse events on which we have based our assessment below can be found in Appendix A. All safety events will be recorded using current UHS templates as per local procedure.

6.1 Adverse event (AE) recording & reporting:

For purposes of this protocol:

- All AEs will be recorded at participant visits or ad hoc phone calls with the participant and the research nurse and categorised as to expectedness, relatedness and severity.
- All non-solicited AEs will be reported. Depending on the nature of the event, the reporting procedures below should be followed. Any questions concerning adverse event reporting will be directed to the Chief Investigator in the first instance.
    - Adverse Events form is sent to the Chief Investigator
    - Severity of AEs will be graded on a three-point scale (mild, moderate, and severe).
    - Relation (causality) and seriousness of the AE to the treatment will be assessed by the Chief Investigator.

6.1.1 Definitions of Solicited AEs:

The adverse event (AE) most likely to occur in this study is bladder discomfort. This is a study outcome and therefore will not be reported. Other potential AEs are listed in Table 2. As with bladder discomfort these AEs will be recorded but not reported.

Table 2 Solicited Adverse Events (AEs)

Relationship	Description
POSSIBLE	Urinary leakage
POSSIBLE	Bladder discomfort
POSSIBLE	Catheter blockage
POSSIBLE	Haematuria
POSSIBLE	Accidental Removal
Yes	Valve not opening

6.1.2 Specific actions following Adverse Events:

Participant advised to stop using the valve:

- If symptoms suggest a urinary tract infection advise the participant to send a urine sample to their GP
- Participant reverts to usual form of urinary catheter

- If no further symptom reported, then participant resumes testing the valve after two weeks if participant wishes
- If symptom recurs, participant to be withdrawn

6.2 Serious Adverse event (SAE) recording & reporting

For purposes of this protocol:

- All SAEs will be recorded throughout the duration of the trial until two weeks after the participant completes the study.
- All non-solicited SAEs during study participation will be reported to the Chief Investigator within 24 hours of the research nurse learning of its occurrence using an Adverse Events form. In the case of incomplete information at the time of initial reporting, all appropriate information should be provided as follow-up as soon as this becomes available.
- Relationship of the SAE to study procedures will be assessed by the Chief Investigator, as should the expected or unexpected nature of the SAE.
- All non-solicited SAEs will be reported by the Chief investigator (or delegated member of the team) to the sponsor with 24 hours of becoming aware. All information is to be sent to rgoinfo@soton.ac.uk.
- Relevant ethics committees and regulatory bodies will also be notified as required.

6.1.3 Definitions of Solicited SAEs:

The following SAE's are regarded as solicited; these events will be recorded but not reported.

- Any pre-planned hospitalisations (e.g. elective surgery) not associated with clinical deterioration.
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- Elective or scheduled treatment for pre-existing conditions that did not worsen during the study.

6.3 Safety Stopping Criteria

If none of the first 4 participants have successfully completed protocol (in either day 1 or day 2), the trial will be stopped.

In case of occurrence of an SAE considered to be at least possibly related to trial or in case of two severe or clinically significant AEs considered to be at least possibly related to the trial, the study will be halted. The trial will only be re-started following an internal review of safety.

Clinically significant adverse events are:

- Accidental dislodgement of urinary catheter during intervention.
- The requirement to change the urinary catheter.
- New bladder or pelvic pain not resolved by the removal of the valve.

7. STUDY QUALITY & MANAGEMENT PROCEDURES

7.1 Investigator Procedures

Approved site-specific SOPs will be used at all clinical and laboratory sites.

7.2 Monitoring

The sponsor will maintain oversight of all monitoring activity of the trial. All monitoring activities for this trial have been delegated to the Project Management Team, based in the NIHR Clinical Research Facility, University Hospital Southampton. All monitoring activity will be performed by the delegated party as per the trial monitoring plan, according to International Conference on Harmonisation (ICH) Good Clinical Practice (GCP).

Following written standard operating procedures, the monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements. The investigator sites will provide direct access to all trial related source data/documents and reports for the purpose of monitoring and auditing by the sponsor and inspection by local and regulatory authorities.

7.3 Quality Control, Quality Assurance and statutory inspection

The UHS R&D department QA staff will provide Quality Assurance (QA) for the trial and perform internal audits to check that the trial is being conducted, data recorded, analysed and accurately reported according to the protocol, study SOPs and in compliance with ICH GCP. The audits will also include laboratory activities according to an agreed audit schedule. The internal audits will supplement the sponsor's monitoring process and will review processes not covered by the sponsor's monitor.

The Sponsor, trial site and ethical committee may carry out audit to ensure compliance with the protocol, GCP and appropriate regulations. GCP inspections may also be undertaken by the regulatory authority to ensure compliance with protocol and national regulations. The sponsor will assist in any inspections.

7.4 Clinical investigation plan amendments

Amendments to the clinical investigation plan must be submitted to the Sponsor for review before submitting to the appropriate REC, Regulatory Authority and local R&D for approval.

7.5 Clinical investigation plan violations, deviations and serious breaches

The CI will not implement any deviation from the clinical investigation plan without agreement from the Sponsor, except where necessary to eliminate an immediate hazard to clinical investigation participants.

In the event that the CI needs to deviate from the clinical investigation plan, the nature of and reasons for the deviation will be recorded on a safety event form using current

UHS templates, as per local procedure. The sponsor will be notified and CAPA forms will them be completed and signed off by sponsor as necessary.

If this necessitates a subsequent clinical investigation plan amendment, this will be submitted to the Sponsor for approval and then to the appropriate REC, Regulatory Authority and local NHS R&D for review and approvals as appropriate.

In the event that a serious breach of GCP is suspected, this will be reported to the Sponsor immediately. Relevant ethics committees and regulatory bodies will also be notified as required.

7.6 Clinical investigation record retention

All clinical investigation documentation will be kept retained and stored in line with local site policies and procedures. When the minimum retention period has elapsed, clinical investigation documentation will not be destroyed without permission from the sponsor.

7.7 End of clinical investigation

The end of clinical investigation is defined as 2 weeks after the last participant's last visit (LPLV). This is in line with the safety reporting parameters for this study.
The Investigators and/or the clinical investigation steering committee and/or the sponsor have the right at any time to terminate the clinical investigation for clinical or administrative reasons.

The end of the clinical investigation will be reported to the REC and Regulatory Authority within 90 days, or 15 days if the clinical investigation is terminated prematurely. The Investigators will inform participants of the premature clinical investigation closure and ensure that the appropriate follow up is arranged for all participants involved.

A summary report of the clinical investigation will be provided to the REC and Regulatory Authority within 1 year of the end of the clinical investigation.

8. ETHICS

8.1 Declaration of Helsinki

The Investigator will ensure that this clinical investigation is conducted in full conformity with the current revision of the Declaration of Helsinki (last amended October 2000, with additional footnotes added 2002 and 2004).

8.2 ICH guidelines for good clinical practice

The Investigator will ensure that this clinical investigation is conducted in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996.

8.3 Approvals

The clinical investigation plan, informed consent form, participant information sheet and any proposed advertising material will be submitted to the Sponsor, an appropriate Research Ethics Committee (REC), regulatory authorities, and host institution(s) for written approval.
The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

8.4 Participant confidentiality

The clinical investigation staff will ensure that the participants' confidentiality is maintained. The participants will be identified only by initials and a participants ID number on the paper CRF and study database. All documents will be stored securely and only accessible by clinical investigation staff and authorised personnel.

9. DATA HANDLING AND RECORD KEEPING

9.1 Data Handling

The chief investigator will be responsible for delegating the receiving, entering, cleaning, querying, analysing and storing of all data that accrues from the study.

The Trial Master File (TMF) will be held and managed in the Southampton NIHR Clinical Research Facility, in a secure location.

The investigators and research team will enter the visit data on to the volunteers' case report form(s) (CRFs), which will be in a paper format. Visit data will then be transcribed from CRFs to the study database (Excel spreadsheet), which will be retained in accordance with the University of Southampton's Research Data Management policy. Transcription of data from CRFs to the electronic database will be checked by the study monitor.

9.2 Record keeping

The investigators will maintain and retain appropriate medical and research records and essential documents for this trial in compliance with ICH GCP and regulatory and institutional requirements for the protection of confidentiality of volunteers.

The chief investigator, co-investigators and clinical research staff will have access to records. The investigators will permit authorised representatives of the sponsor, regulatory agencies and the monitors to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

9.3 Source data and case report forms (CRFs)

All protocol-required information will be collected in CRFs designed by the investigator.

All source documents, excluding hospital records, will be filed in TMF.

Source documents are original documents, data, and records from which the volunteer's CRF data are obtained. For this study these will include, but are not limited to; volunteer consent form, the medical file of the volunteer, GP response letters and correspondence. In the majority of cases, CRF entries will be considered source data as the CRF will be the site of the original recording (i.e. there is no other written or electronic record of data). In this study this will include, but is not limited to, medical history, medication records, vital signs, urine assessments, adverse event data and details of study interventions.

9.4 Data protection

The CIP, documentation, data and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorised third party, without prior written approval of the sponsor. The participants will be identified by a clinical investigation specific participant number and/or code in any database. The name and any other identifying detail will NOT be included in any clinical investigation data electronic file.

10. FUNDING AND INSURANCE

10.1 Funding

This trial will be funded by the National Institute for Health Research (NIHR) under the Invention for Innovation (i4i) scheme.

10.2 Insurance

The University of Southampton has a specialist insurance policy in place, which would operate in the event of any participant suffering harm as a result of their involvement in the research.

11. REFERENCES

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12. APPENDICES

APPENDIX A – ADVERSE EVENTS DEFINITIONS

Any untoward medical occurrence in a subject to whom a study intervention or procedure has been administered, including occurrences which are not necessarily caused by or related to that intervention. An AE, therefore, does not necessarily have a causal relationship with the treatment. In this context, "treatment" includes all interventions administered during the course of the study. Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment.

Related AE: An AE that results from administration of any of the research study procedures. All AEs judged by either the reporting investigator or the sponsor as having reasonable causal relationship to a study procedure qualify as 'related adverse events'. The expression "reasonable causal relationship" means to convey in general that there is evidence or argument to suggest a causal relationship.

Causality: The assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in the table below. All adverse events judged as having a reasonable suspected causal relationship to a study procedure (i.e. definitely, probably or possibly related) are considered to be related adverse events. If any doubt about the causality exists, the local investigator (PI) should inform the Chief Investigator. In the case of discrepant views on causality between the investigator and others, all parties will discuss the case. In the event that no agreement is made, the main REC and other bodies will be informed of both points of view.

Table 1 - Categorisation of causality of an observed adverse event

Relationship	Description
Unrelated	There is no evidence of any causal relationship
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the study procedure). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the study procedure). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

Unexpected Adverse Event: An adverse event that is not listed in the study protocol as an expected occurrence in the circumstances of this trial.

Serious Adverse Event (SAE): an untoward occurrence (whether expected or not) that:-

- Results in death
- Is life-threatening (refers to an event in which the subject 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
- Consists of a congenital anomaly or birth defect
- Is otherwise considered medically significant by the investigator

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important medical events that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

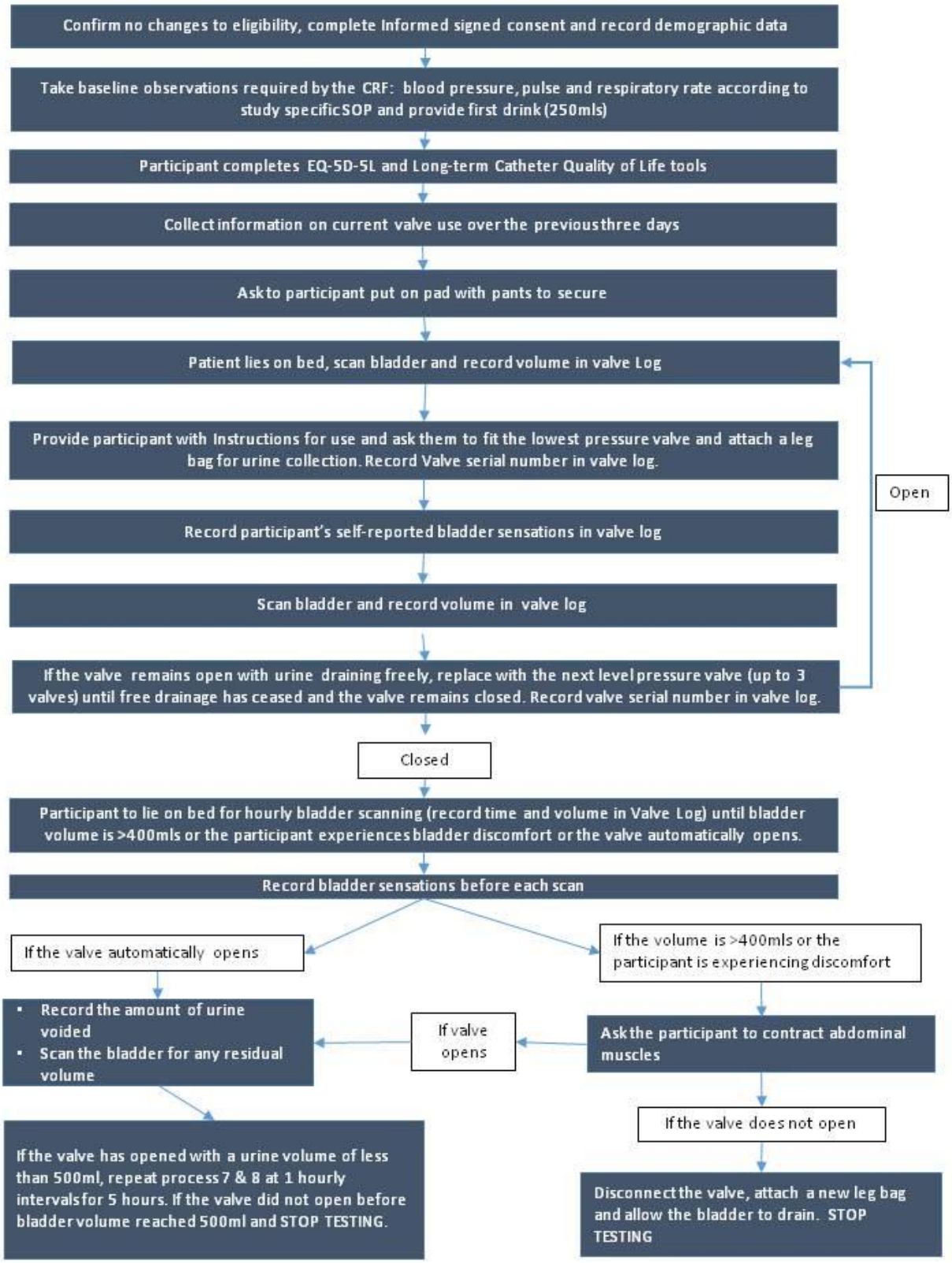
Severity (intensity) of Adverse Events and Adverse Reactions

Severity of all AEs will be graded on a three-point scale of intensity (mild, moderate, severe):

- Mild: Discomfort is noticed, but there is no disruption of normal daily activities.
- Moderate: Discomfort is sufficient to reduce or affect normal daily activities.
- Severe: Discomfort is incapacitating, with inability to work or to perform normal daily activities.

An AE may be severe but not serious.

APPENDIX B – TRIAL PROCEDURES: DAY 1



APPENDIX C – TRIAL PROCEDURES: DAY 2