Clinical Investigation Plan

CP334

A confirmatory, multi-centre, randomised, open label, controlled study confirming performance of a single-use intermittent micro-hole zone catheter in a population of adult male intermittent catheter users.

August 2022 – January 2023

Date: 2023-03-24

NCT05485935

CHANGE LOG

VERSION NUMBER	ISSUED BY *(INITIALS)*	COMMENTS (MAJOR CHANGES SINCE LAST REVISION)
1.0	[redacted]	
2.0	[redacted]	• Sec 6.6: Reference to section 13.1.1. – corrected into 12.1.1 • Sec 6.2.6: leukocyturia and specific gravity added • Appendix A added
3.0	[redacted]	Correction of flowchart formatting
4.0	[redacted]	Typos and minor corrections to ease understanding
5.0	[redacted]	Assessment "Other" added in section 6.2.5 due to analysis method

Synopsis of the clinical investigation

Title:

A confirmatory, multi-centre, randomised, open label, controlled study confirming performance of a single-use intermittent micro-hole zone catheter in a population of adult male intermittent catheter users.

Test device and comparator:

The investigational device (test device) is a catheter for single use only and is intended to be used for drainage of the bladder through the urethra. The device is a new flexible single-use intermittent micro-hole zone catheter, which comes in two different sizes - size CH12 and CH14 - for male catheter users. The devices will be provided by Coloplast A/S, Denmark.

The comparator will be single-use hydrophilic sleeved soft/flexible catheters, of brand/type Hollister VaPro or Coloplast SpeediCath Flex, in the sizes CH12 or CH14. As the comparator devices are already on the market and will be used within the intended use in this investigation, it is not considered an investigational device.

Intended use:

The investigational device is a urinary catheter for intermittent use, available in the sizes CH12 and CH14. The catheter is intended for transient (less than 60 minutes) intermittent drainage of the bladder.

Objectives:

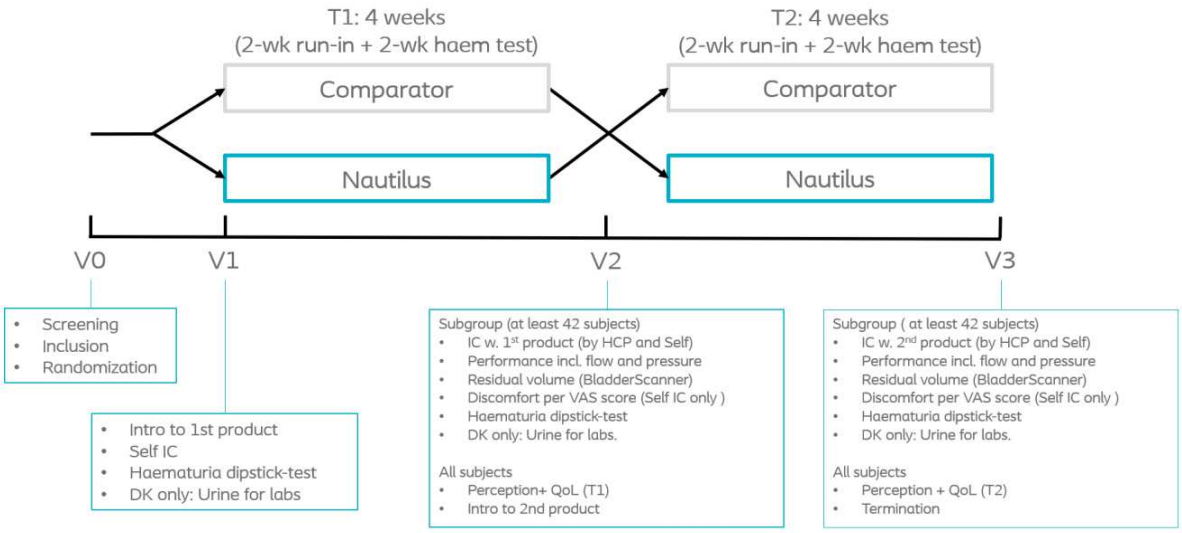
The primary objective is to demonstrate superior performance of the micro-hole zone catheter compared to a conventional 2-eyelet catheter through an improved bladder emptying.

The second objective is to demonstrate reduced hematuria as a surrogate of reduced catheter-associated micro-trauma with the micro-hole zone catheter compared to a conventional 2-eyelet catheter.

The exploratory objective is to assess catheter perception and health-related quality of life with the micro-hole zone catheter compared to a conventional 2-eyelet catheter.

Design of the investigation:

A multi-centre, randomised, controlled crossover design. The total study duration for the individual subject will be approximately 9 weeks, consisting of four site visits and two 4-week test periods at home. Visits 0 and 1 can be performed on the same day. For visit 2 and 3, catheterisations will be performed in a hospital setting for bladder emptying assessment and collection of urine samples (the latter only in Denmark). Visit 1 and 2 are followed by a home-use test period, followed by visit 3 which terminates the study. The design is given in this figure:



Expected duration of the clinical investigation:

No subjects will be enrolled before all required approvals have been obtained. If changes are required, applicable EC and regulatory authorities will be notified. The following dates are approximate:

First patient in (FPI)	August 2022
Last patient in (LPI)	October 2022
Last patient out (LPO)	December 2022
Database lock (DBL)	January 2023

Endpoints:

Primary endpoints

- Residual volume at 1st flow-stop (RV1) i.e., post catheterisation volume minus volume at 1st flow-stop, both derived from a catheterisation profile, measured at visit 2 and 3 (HCP-catheterisation), [g].
- Number of flow-stop episodes derived from a catheterisation profile, measured at visit 2 and 3 (HCP-catheterisation), [count].

Secondary endpoint

- Red blood cell concentration collected during the final two weeks of T1 and T2 (response based on dipstick test), [Eryt/µL].
- Number of positive haematuria occurrences collected during the final two weeks of T1 and T2 (binary response based on dipstick test), [positive/negative scale].

Supportive secondary endpoints

- Residual volume at 1st flow-stop (RV1) i.e., post catheterisation volume minus volume at 1st flow stop, both derived from a catheterisation profile, measured at visit 2 and 3 (self-catheterisation), [g].
- Number of flow-stop episodes derived from a catheterisation profile, measured at visit 2 and 3 (self-catheterisation), [count].

Exploratory endpoints

- Pressure measurement at 1st flow-stop derived from a catheterisation profile (self-catheterisation), [mbar].
- Pressure measurement at 1st flow-stop derived from a catheterisation profile (HCP-catheterisation), [mbar].
- Average from 3 consecutive measurements of residual volume post catheterisation measured with a bladder scanner (self-catheterisation), [mL].
- Average from 3 consecutive measurements residual volume post catheterisation measured with a bladder scanner (HCP-catheterisation), [mL].
- Discomfort at insertion of catheter measured on a VAS (self-catheterisation).
- Discomfort during emptying of bladder measured on a VAS (self-catheterisation).
- Discomfort at end of emptying the bladder measured on a VAS (self-catheterisation).
- Discomfort at withdrawal measured on a VAS (self-catheterisation).
- QoL Index score (Qualiveen questionnaire), assessed at V2 and V3.
- Perception questionnaire evaluated on a 5-point scale assessed at V2 and V3.

Population/subjects to be included

The clinical investigation will be conducted in 72 male IC users above the age of 18 years and no upper age limit enrolled at multiple clinical investigation sites.

The recruitment should aim towards a population distribution of 40-60% between users with neurological bladder dysfunction and non-neurological bladder dysfunction and also an aim to have a 50/50 split between SpeediCath Flex and Vapro users.

To be included in the investigation, the subjects must comply with the selection criteria described below:

Inclusion criteria	Justification for inclusion criteria
1. **Male**	Intended patient population of investigational and comparator devices.
2. **Is at least 18 years of age and has full legal capacity**	Intended patient population of investigational and comparator devices. To meet Helsinki Declaration
3. **Has given written informed consent**	To ensure that the subject has been given written and oral information regarding the investigation and know enough about the investigation to decide on participation. To ensure voluntariness and that Helsinki Declaration is met.
4. **Has signed letter of authority (only DK)**	Letter of Authority is a demand from Danish Medicines and Health Authorities
5. **Has used clean intermittent self-catheterisation (CISC) for at least the last 3 months**	To ensure standardisation of handling/training in intermittent catheters
6. **Has used intermittent catheterisation as the only bladder emptying method for at least the last 3 months**	To ensure standardisation of handling/training in intermittent catheters
7. **Self-catheterise using Coloplast SpeediCath Flex or Hollister VaPro catheters, CH12 or CH14, for at least 3 months prior to inclusion**	To ensure standardisation of handling/training in the use of single-use hydrophilic sleeved soft/flexible intermittent catheters. The chosen brands/type are representative of this kind of catheters and estimated to correspond to the largest market shares in the countries where the study will be conducted.
8. **Ability (assessed by investigator) and willingness to adhere to a 2-month study period**	To ensure sufficient data for successful completion of the study.

Exclusion criteria	Justification for exclusion criteria
1. **Participation in any other clinical study during this investigation**	To eliminate uncertainty whether any Adverse Events (AE's) or Serious Adverse Events (SAE's) occurring during the investigation relate to use of the herein tested devices. Also, to eliminate unintentional effect from other devices/medicines on the investigation's data.
2. **Previous participation in this study**	
3. **Symptoms of urinary tract infection as judged by the investigator (rescheduling allowed within recruitment period for LPI)**	To ensure subject safety and integrity of results.
4. **Individuals with history, suspected or showing signs of producing urine with excessive amount of mucus or large/clustered sediments or debris**	To ensure subject safety and integrity of results.
5. **Any known allergies towards ingredients in the investigational device**	To ensure subject safety and integrity of results.

Investigational approval

The investigation will be approved by the relevant Ethical Committees and Competent Authorities in the participating countries before investigation initiation.

1 List of abbreviations and definitions

ABBREVIATION	WRITTEN OUT	EXPLANATION
ADE	Adverse Device Effect	See section 19.2
AE	Adverse Event	See section 19.1
ASADE	Anticipated Serious Adverse Device Effect	See section 19.4.2
-	Catheterisation profile	Catheterisation profile: Graphical presentation of urine pressure and volume over time, measured with a pressure sensor connected to the catheter and the urine volume recorded on a time logged scale
CIP	Clinical Investigation Plan	
CRF	Case Report Form (paper or electronic)	Data capture form to be used for data collection
CRO	Clinical Research Organisation	
CM	Clinical Manager	
DQF	Data Query Forms	A DQF is a query specifically used in clinical research. The DQF is the primary data query tool from the sponsor to clarify discrepancies and ask the investigator for clarification. The DQF is part of the data validation process in a clinical investigation.
DD	Device deficiency	
-	Enrolment	The process of registering or entering a patient into a clinical trial. Once a patient has been enrolled, the participant would then follow the clinical trial protocol
EC	Ethics Committee	
FAS	Full Analysis Set	
FS	Flow Stop defined by HCP	Flow stop defined by HCP is the nurse's subjective judgment of when the catheter stops draining the bladder.
HCP	Healthcare professional	
IB	Investigator's Brochure	Compilation of the current clinical and non-clinical information on the investigational medical device(s,) relevant to the clinical investigation.
IC	Intermittent catheterization	
IFU	Instruction For Use	
-	Included subject	An enrolled subject that fulfils in- and exclusion criteria can be randomised and is included in the study.
ITT	Intention to Treat	
LUTD	Lower urinary tract diseases	
MITT	Modified Intention to Treat	
OR	Odds Ratio	
PI	Principal Investigator	
PP	Per Protocol	Qualified person responsible for conducting the clinical investigation at an investigation site. If the clinical investigation is conducted by a team of individuals at an investigation site, the PI is the responsible leader of the team. Whether this is the

		responsibility of an individual or an institution can depend on national regulations.
-	Pre-screening	Pre-screening is the term used to describe activities performed before obtaining informed consent and before enrolment.
-	Profile-derived flow stop	Profile-derived flow stop is the flow stop determined via the pressure and flow curve recorded by the measurement device.
-	Randomisation	The process by which participants in clinical trials are assigned by chance to separate groups that are given different treatments.
-	Replaced subject	A subject included in the study, that – for some reason – decides to withdraw his participation, can be replaced, meaning that a new subject can replace him.
RR	Risk Ratio	
RV1	Residual urine volume at 1st flow stop	
SADE	Serious Adverse Device Effect	See section 19.4.1
SAE	Serious Adverse Event	See section 19.4
SD	Standard Deviation	See section 11.8
-	Screening	Screening is the term used to describe activities performed after obtaining consent to ensure subjects are qualified for the study.
SF	Screen Failure	A subject that does not fulfil the in- and exclusion criteria
SG	Specific gravity	Urine specific gravity is a measure of urine concentration. Specific gravity measurements are a comparison of the number of substances dissolved in urine compared to pure water. If there were no substances present, the specific gravity of the urine would be 1 (the same as pure water). Since all urine has some substances in it, a urine SG of 1 is not possible. If a person drinks large quantities of water in a short period of time, then the urine SG may be very close to that of water.
USADE	Unanticipated serious adverse device effect	See section 19.4.3
UTI	Urinary tract infection	
VAS	Visual analogue scale	

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2 List of personnel involved in the Investigation

COORDINATING CLINICAL MANAGER	DATA MANAGEMENT SPECIALIST
[redacted] dksths@coloplast.dk	[redacted] dkcki@coloplast.com
SENIOR CLINICAL MANAGER	**SENIOR MEDICAL WRITER**
[redacted] dkhros@coloplast.com	[redacted] dkmhla@coloplast.com
PRINCIPAL MEDICAL AFFAIRS PROJECT MANAGER	**SENIOR BIOSTATISTICIAN**
[redacted] dkomar@coloplast.com	[redacted] dklja@coloplast.com

In case of emergency, please contact the Clinical Manager from the above list of sponsor representatives - please choose only one.

All tasks done at the site, not done by the principal investigator, will be documented on the Site Personnel Signature and Delegation List.

3 Rationale/justification for conducting the clinical investigation

Urinary tract infections (UTIs) are a common sequela in individuals with lower urinary tract diseases (LUTD) who are dependent on urinary catheters for bladder emptying (Averbeck et al., 2018; De Ridder et al., 2005; Feneley, Hopley, & Wells, 2015; Kennelly et al., 2019; Wyndaele, 2002). Although clean intermittent catheterisation (IC) is considered one of the safest drainage methods, the incidence of catheter associated UTI is still high with rates between 0.8-3.5 per year (Kennelly et al., 2019). Common risk factors from IC include urethral and bladder trauma, incomplete bladder emptying and bacterial insertion supporting an environment for infection (Averbeck et al., 2018; Fisher et al., 2018; Kennelly et al., 2019).

Therefore, Coloplast A/S is in the process of developing a new intermittent micro-hole zone catheter for males, to ensure thorough bladder emptying without the need for repositioning and with minimal urethral and bladder trauma.

The aim of this investigation is to assess performance of this new micro-hole zone catheter.

4 Objectives and hypotheses of the clinical investigation

4.1 Primary objective

To demonstrate superior performance of the micro-hole zone catheter compared to a conventional 2-eyelet catheter through an improved bladder emptying.

4.2 Secondary objectives

To demonstrate reduced hematuria as a surrogate of reduced catheter-associated micro-trauma with the micro-hole zone catheter compared to a conventional 2-eyelet catheter.

4.3 Exploratory objectives

To assess catheter perception and health-related quality of life with the micro-hole zone catheter compared to a conventional 2-eyelet catheter.

4.4 Hypotheses

The aim is to assert the hypothesis of superior performance of the micro-hole zone catheter compared to a conventional 2-eyelet catheter.

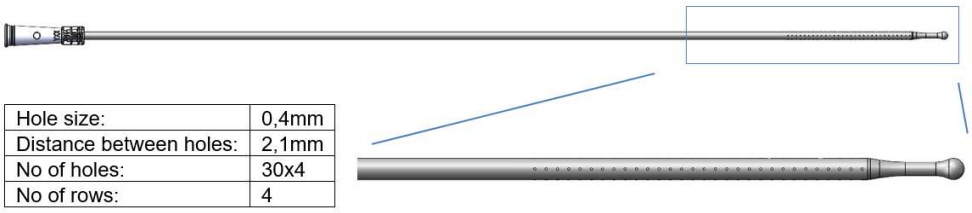
5 Investigational device and comparators

5.1 Description of investigational device

The investigational device is a ready-to-use, sterile, hydrophilic-coated male catheter for intermittent catheterisation. The device is for single use only and is intended to be used for drainage of the bladder through the urethra by people with missing or reduced bladder control.

The investigational device has a flexible tip (Flex tip) that facilitates passage through the sphincter in the urethra and is compositionally identical to the already CE-marked SpeediCath® Flex. The only difference is the design and manufacturing method of the drainage holes. The SpeediCath® Flex catheter has two oval holes by the tip used for voiding while the investigational devices have several smaller micro-hole by the tip, creating a drainage zone. The hole punch process for the current SpeediCath® Flex catheter is exchanged with a laser cut process to accommodate for the smaller micro-hole size.

Figure 5-1 illustrates the micro-hole zone catheter used as investigational device in this study.



Hole size:	0,4mm
Distance between holes:	2,1mm
No of holes:	30x4
No of rows:	4

Figure 5-1 Micro-hole zone catheter and corresponding information

The device is intended to be used by male catheter users in this clinical study.

The investigational device includes a coating system to reduce surface friction. A sleeve around the investigational device keeps the coating and catheter sterile through insertion.

The drainage end of the investigational device has an outlet to which a urine bag with a suitable connector can be connected. At the end of the sleeve there is a guide tip to help protect the user not to touch the catheter shaft and make it easier to insert the catheter.

The primary packaging provides the sterile barrier of the investigational device and contains tear opening as a proof of seal for identification of used devices. All legally required information is presented on the investigational device primary packaging.

The investigational devices are sterile by radiation.

The investigational devices are not CE-marked.

5.2 Manufacturing

Responsible for manufacturing the investigational device:

Coloplast A/S
Holtedam 1
3050 Humlebæk
Denmark.

5.3 Identification and traceability of the device

All investigational devices (non-CE marked test devices) are labelled as per regulations and include “Exclusively for Clinical Investigational” on the label. The devices are also identified with study number, device name/code, and item/lot number and is accounted for through a master sponsor accountability log.

Figure 5-2 illustrates the labels for the investigational devices.

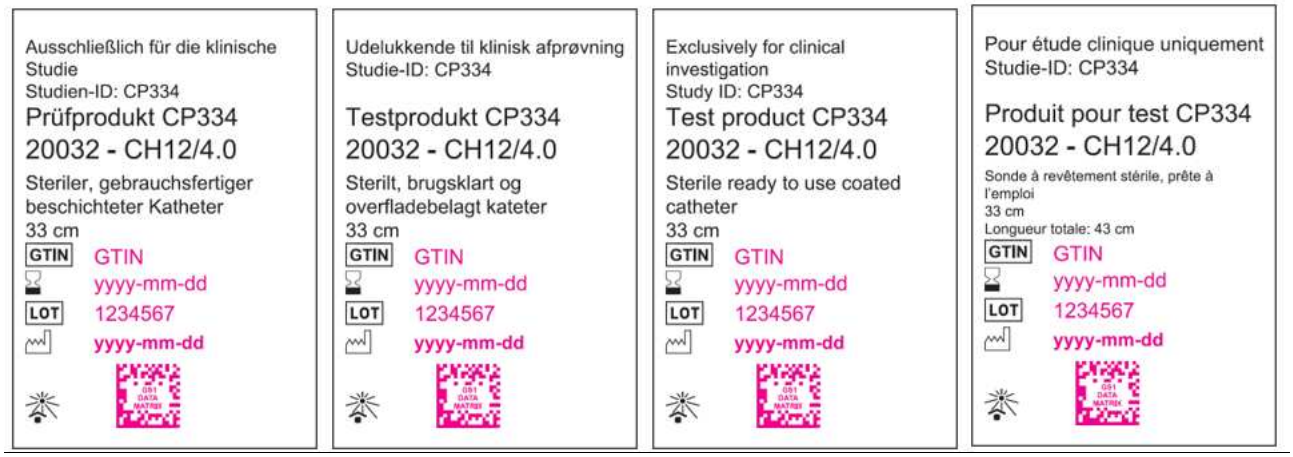


Figure 5-2: Labels for the investigational devices for male catheters size CH12 (left to right: German, Danish, English, and French). Labels for CH14 only varies with regards to printed CH-size and item number.

Upon EC and CA approval (Regulatory Greenlight) , investigational devices will be shipped to the principal investigator, or designee. Additionally, all investigational devices will be accounted for and documented on a site accountability log. The receipt and disposition of all investigational devices will be verified through monitoring. All unused devices will be returned to Coloplast at the conclusion of the study.

5.4 Intended use of the device in the clinical investigation

The investigational device is a urinary catheter for intermittent use, available in the sizes CH12 and CH14.

The catheter is intended for transient (less than 60 minutes) intermittent drainage of the bladder.

5.5 Intended population for the device

The eligible population is male intermittent catheter (IC) users who are depending on IC for drainage of the bladder. This population will be eligible to use the newly developed device when it becomes commercially available.

There are no proposed contraindications.

5.6 Handling of the investigational device

The handling of the investigational device is described in detail in the Instruction for Use (IFU) accompanying the devices. It is stated in the IFU that the investigational devices are for single-use and must be stored away from direct sunlight. Reprocessing, washing, disinfection, and sterilisation may compromise device characteristics, causing additional risk of physical harm to or infection of the user.

All Principal Investigators, and designees will receive training by the sponsor and/or principal investigator in the handling and correct use of the investigational devices. The Principal Investigator, or designee, will train the subjects in the correct use of the investigational devices. All training will be documented.

For further details regarding the test device, please refer to the Investigators Brochure (VV-0355661).

5.7 Total number of devices intended for the clinical investigation

Seventy-two subjects will be included in the study. The test period (home-use) is 4 weeks (28 days) and with a use of 6 catheters/day, the total use is 12.096 units.

Table 5-1 presents an overview of devices needed in this investigation.

Table 5-1: Overview of devices needed in the investigation

Device	Description
Investigational device 1	Intermittent catheter for male use – size CH12
Investigational device 2	Intermittent catheter for male use – size CH14
Investigational device for hospital assessments	Investigational device to be used for hospital assessments will be provided by Coloplast A/S
Comparator device for hospital assessments	Comparator device to be used for hospital assessments will be provided by Coloplast A/S

Use of catheters during study visits will be 72 subjects conducting three visits, using two catheters per visit resulting in a total of 432 units.

A 20%-buffer is added accounting for different sizes, number of sites, etc. Therefore, 15.034 units are required, split per size and country as follows if subjects are equally split between participating countries:

Size/Country	**Germany**	**Denmark**	**France**	**United Kingdom**
CH12	1880	1880	1880	1880
CH14	1880	1880	1880	1880

Please note that the numbers are estimates.

5.8 Description of the comparator device(s)

The comparator will be single-use hydrophilic sleeved soft/flexible catheters as defined below. For home use it will be SpeediCath Flex in the sizes CH12 or CH14 or VaPro, VaPro Pocket, VaPro Plus or VaPro Plus Pocket (all VaPros in sizes 20 or 40 cm). If more than one device is used at home, it will be the primary device (the device that is used the most) that will be considered the comparator device.

For assessments at study visits SpeediCath Flex in the sizes CH12 or CH14 and VaPro 40 cm will be used. As the comparator devices are already on the market and will be used within the intended use in this investigation, it is not considered an investigational device according to ISO 14155:2020 and is thus not described into further details here.

Coloplast will not provide comparator devices for home use.

Devices to be used at study visits will be provided by Coloplast A/S.

To ensure that the site has enough supplies, more investigational devices than needed will be provided by Sponsor to the site. All investigational devices will be accounted for both prior to and after use.

6 Design of the clinical investigation

6.1 General

The investigation is a multi-centre, randomised, controlled crossover study including 72 male IC users. The study will be conducted in Denmark, France, Germany and United Kingdom.

All subjects will have endpoints related to hematuria, catheter perception and quality of life measured during two periods of home-use (test period T1 and T2), while a subgroup of at least 42 subjects will have endpoints related to bladder emptying (residual volume and number of flow-stop episodes), measured at test visits (V2 and V3) at the hospital. Please refer to section 11.8 for further information on sample size.

The total study duration for the individual subject will be approximately nine weeks, consisting of four study visits and two 4-week test periods at home. Visits 0 and 1 can be performed on the same day. For visit 2 and 3, catheterisations will be performed in a hospital setting for bladder emptying assessment (for the above-mentioned subgroup) and urine samples collected (the latter only in Denmark). Visit 1 and 2 are followed by a home-use test period (T1 and T2, respectively), followed by visit 3 which terminates the study.

If the pandemic continues, home visits may be implemented if accepted by the subjects.

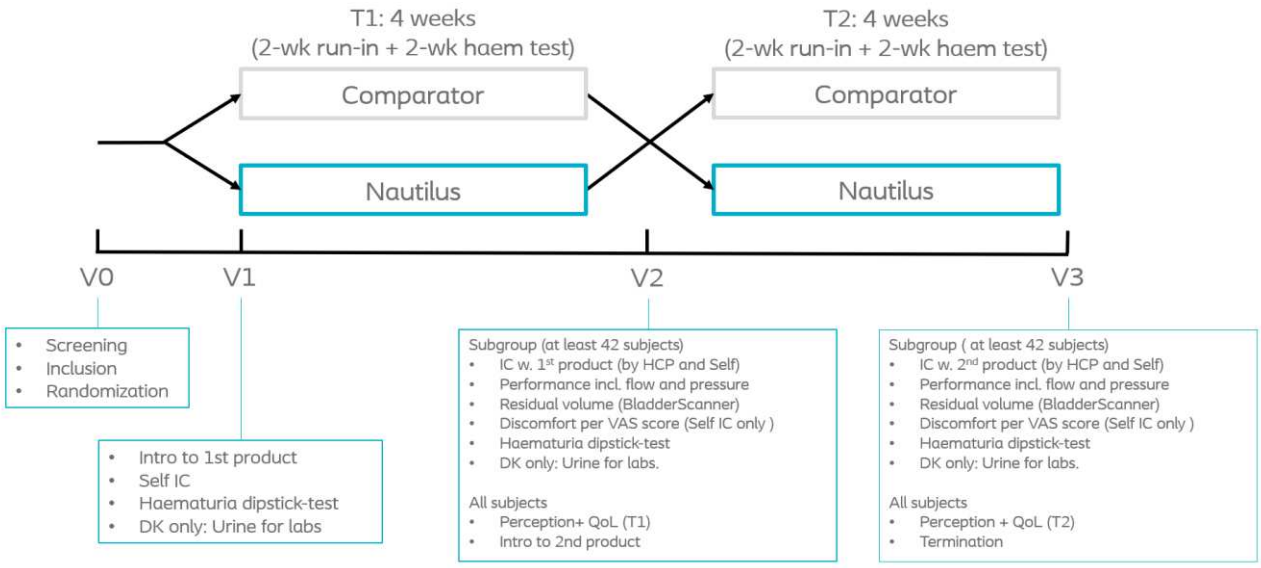


Figure 6-1 Crossover investigation with two devices.

6.2 Endpoints and assessments

6.2.1 Primary endpoints

- Residual volume at 1st flow-stop (RV1) i.e., post catheterisation volume minus volume at 1st flow-stop, both derived from a catheterisation profile, measured at visit 2 and 3 (HCP-catheterisation), [g].
- Number of flow-stop episodes derived from a catheterisation profile, measured at visit 2 and 3 (HCP-catheterisation), [count].

6.2.2 Secondary endpoints

- Red blood cell concentration collected during the final two weeks of T1 and T2 (response based on dipstick test), [Eryt/µL] - (see section 6.5).
- Number of positive haematuria occurrences collected during the final two weeks of T1 and T2 (binary response based on dipstick test), [positive/negative scale] - (see section 6.5).

6.2.3 Supportive secondary endpoints

- Residual volume at 1st flow-stop (RV1) i.e., post catheterisation volume minus volume at 1st flow stop, both derived from a catheterisation profile, measured at visit 2 and 3 (self-catheterisation), [g].
- Number of flow-stop episodes derived from a catheterisation profile, measured at visit 2 and 3 (self-catheterisation), [count].

6.2.4 Exploratory endpoints

- Pressure measurement at 1st flow-stop derived from a catheterisation profile (self-catheterisation), [mbar].
- Pressure measurement at 1st flow-stop derived from a catheterisation profile (HCP-catheterisation), [mbar].
- Average from three consecutive measurements of residual volume post catheterisation in hospital setting measured with a bladder scanner (self-catheterisation), [mL].
- Average from three consecutive measurements of residual volume post catheterisation in hospital setting measured with a bladder scanner (HCP-catheterisation), [mL].
- Discomfort at insertion of catheter measured on a VAS (self-catheterisation).
- Discomfort during emptying of bladder measured on a VAS (self-catheterisation).
- Discomfort at end of emptying the bladder measured on a VAS (self-catheterisation).
- Discomfort at withdrawal measured on a VAS (self-catheterisation).
- QoL Index score (Qualiveen questionnaire) assessed at V2 and V3.
- Perception questions evaluated on a 5-point scale assessed at V2 and V3 in (perception questionnaire).

6.2.5 Assessments collected in hospital setting

For HCP- and self-catheterisations:

- Position of the subjects when performing the catheterisation, [wheelchair, toilet, bed, standing, other (text)].
- Urine volume at 1st flow stop (scale), [g].
- Urine volume measured post catheterisation (scale), [g].
- Urine volume at 1st flow stop derived from a catheterisation profile, [g].
- Urine volume measured post catheterisation derived from a catheterisation profile, [g].
- Pressure at 1st flow stop derived from a catheterisation profile, [mbar].
- Pressure at 1st flow stop derived from a manual worked pedal, marked by HCP [timestamp].
- Urine volume at 2nd until 10th flow stop derived from a catheterisation profile, [g].
- Dipstick haematuria post catheterisation (see section 6.5).
- Dipstick leukocyturia post catheterisation (see section 6.5).
- Dipstick specific gravity (see section 6.5).

- Time for start of catheterization marked by HCP on pressure sensor.
- Biomarkers (35 assessments, DK only, laboratory analysis):

G-CSF – pg/ml	IL-13– pg/ml	Leukocytes – 0, (+), +, ++, +++
GM-CSF– pg/ml	IL-17A– pg/ml	Nitrite – 0, +
IFN-γ– pg/ml	MIP-1β– pg/ml	Urobilinogen – mg/dl
IL-1β– pg/ml	TNF-α– pg/ml	Protein – mg/dl
IL-2– pg/ml	N-GAL– pg/ml	pH – units
IL-4– pg/ml	Albumin – pg/ml	Blood – 0,+/-,2+,+/-,1+,2+,3+
IL-5– pg/ml	B2M– pg/ml	Specific gravity - units
IL-6– pg/ml	Cystatin C– pg/ml	Ketone – mg/dl
IL-7– pg/ml	OsteopoLeucontin TFF3– pg/ml	Bilirubin – 0, +, ++, +++
IL-8– pg/ml	Cell marker uroplakin– pg/ml	Glucose – mg/dl
IL-10– pg/ml	Cell marker KAT14– pg/ml	MCP-1 (MCAF) – pg/ml
IL-12 (p70) – pg/ml	Creatinine – pg/ml	Other

6.2.6 Assessments collected in home setting

- Dipstick haematuria post catheterisation the last 14 days of T1 and T2 (see section 6.5).
- Dipstick leukocyturia and specific gravity post assessed at V1 V2 and V3
- QoL Index score (Qualiveen questionnaire) assessed at V2 and V3.
- Perception questions evaluated on a 5-point scale assessed at V2 and V3 in (perception questionnaire).

6.3 Rationale for selection and measurement of endpoints

The endpoints have been selected based on the evaluation of performance of the new catheter features in terms of efficiency of catheter-associated bladder emptying and degree of catheter-associated microtrauma (the latter via haematuria as a surrogate). Both inadequate bladder emptying and, urethral and urothelial microtrauma, are important risk factors for UTI (Kennelly et al., 2019).

Flow stops: A common process of IC is the repositioning of the catheter towards the end of drainage to ensure thorough bladder emptying (Vahr S., 2013). The rationale behind this process is that as the bladder empties with a standard 2-eyelet catheter, the bladder wall deflates around the drainage holes, causing bladder mucosa to be sucked into the eyelets, withholding urine to exit. In 1965, mucosal suction and consequently mucosal microtrauma was first described with an indwelling Foley catheter (Milles, 1965) and later reproduced in several other settings (Glahn, 1988; Glahn, Braendstrup, & Olesen, 1988; Grocela & Jura, 2010). Recently, the event was reproduced with intermittent catheters in a porcine bladder model in a pre-clinical setting at Coloplast (data not yet published) and lately exploratory clinical activities involving healthy subjects and IC-users (both male and female) have demonstrated a significantly reduced number of flow stops with the new micro-hole zone catheter compared to conventional 2-eyelet catheters (Coloplast A/S, 2021a).

Residual volume at 1st flow stop: As a consequence of mucosal suction, urine flow may come to a halt prematurely, i.e. before the bladder is thoroughly emptied, hence the need to adjust the catheter (e.g. repositioning) to ensure that urine starts to flow again. The aim with the micro-hole drainage zone is to avoid mucosal suction, thereby securing a thorough bladder emptying at the first sensation of a flow stop. Therefore, residual urine volume at 1st flow stop (RV1) represent the volume left in the bladder for those IC-users who perceive a flow-stop as an emptied bladder and therefore withdraws the catheter prematurely. RV1 is a technical/theoretical term and is thought to be a contributing factor to any other residual urine left in the bladder after catheterization (see Figure 6-2).

RV1 is measured during both HCP-catheterisation and self-catheterisation as catheterization by HCP allows the for comparison between catheters during an expectedly correctly applied catheterization technique, while self-catheterisation shed light on what could happen when including some variance by users (i.e., taking different catheterisation techniques between users into account.

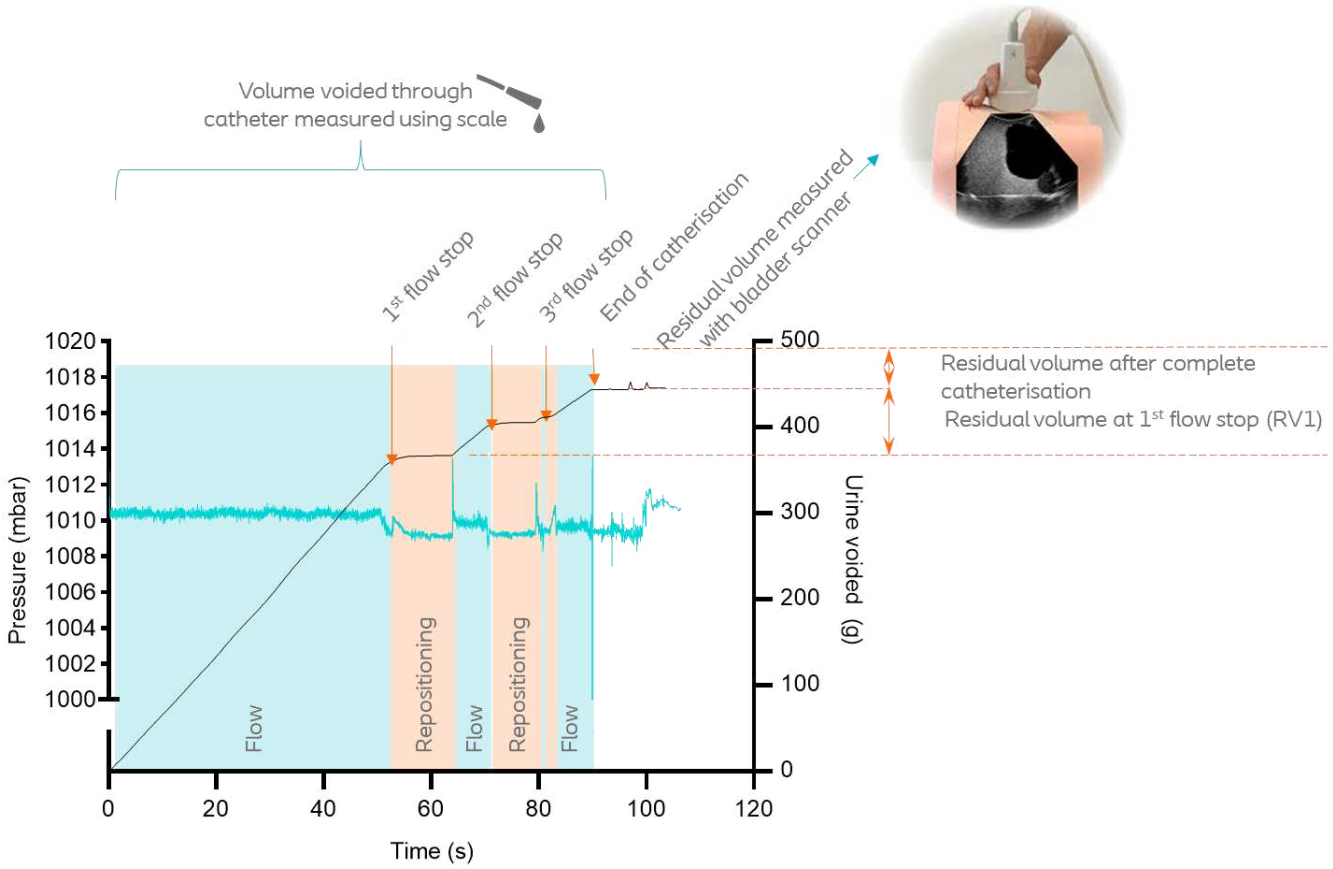


Figure 6-2: Overview of measurements during and after catheterisation.

Microtrauma: Concentration of microscopic haematuria and incidences of positive haematuria indicates possible catheter-associated microtrauma. With the micro-hole zone catheter, fewer mucosal suctions and putatively less or no co-sequential blood in the urine is expected. This is based on previous literature showing mucosal suction and associated trauma with indwelling catheters (Glahn, 1988; Glahn et al., 1988; Grocela & Jura, 2010; Milles, 1965), which has also been demonstrated with conventional 2-eyelet intermittent catheters in the preclinical setting (Coloplast A/S, 2021b, 2021c) (data not yet published).

6.4 Demography and potential compromising factors

The following baseline data will be collected and registered at the screening visit (V0) by the investigator or designee:

- Date of informed consent
- Date of visit
- Age
- For how long time have you used a catheter? (months or years)
- Average number of catheters used per day during the last 3 months
- Current device brand/type (can choose more than one)
    - Coloplast SpeediCath® Flex
    - Hollister VaPro™
    - Hollister VaPro Pocket™
    - Hollister VaPro Plus™

    - Hollister VaPro Plus Pocket™
- Current device size
    - Coloplast SpeediCath® Flex, CH12, CH14
    - Holister VaPro™, 20 or 40 cm
    - Holister VaPro Pocket™, 20 or 40 cm
    - Holister VaPro Plus™, 20 or 40 cm
    - Holister VaPro Plus Pocket™, 20 or 40 cm
- Position most frequently used during catheterisation
    - Wheelchair
    - Toilet
    - Bed
    - Standing
    - Other (text)
- Urethral sensation
    - Normal
    - Impaired
    - None
    - Hypersensitive
- Reason for using IC
    - Spinal cord injury
    - Multiple sclerosis
    - Spina Bifida
    - Benign Prostatic Hyperplasia
    - Others (as text)
- Neurogenic/non-neurogenic
- Body mobility / ambulation (can choose more than one option)
    - Walking
    - Walking with difficulty/aids
    - Using a wheelchair
    - Confined to bed
- How is your handedness?
    - Right-handed
    - Left-handed
    - Mixed or cross-dominant (i.e., changes according to task)
    - Ambidextrous (i.e., equal ability in both hands)
- How would you describe the level of dexterity of your hands?
    - Left hand
        - Normal dexterity
        - Reduced dexterity
        - Greatly reduced dexterity
        - Don’t know
    - Right hand
        - Normal dexterity
        - Reduced dexterity
        - Greatly reduced dexterity
        - Don’t know

- Concomitant medication
- Relevant Medical history

6.5 Equipment/methods and timing for assessing the variables

Supplementing devices or instruments normally used for catheterisation (e.g. medical gloves, tray for urine collection), scales for measurement of total amount of urine, ultrasound scanner measuring residual urine [BladderScan i10, Verathon Inc.], container and funnel for urine collection and pressure sensor to measure flow stops will be provided by Coloplast. Stix used for measuring haematuria in urine in home setting and measuring haematuria, gravity and leukocytopenia at study visits will be provided by Coloplast A/S. Siemens Dip stix for home use will be handed out by the investigational site.

The pressure sensor is an electronic device used for monitoring the pressure near the eyelets of an intermittent urinary catheter during voiding. The pressure sensor comprises a reusable electronic assembly and a single use sensor. The sensor parts will not have direct nor indirect contact to the end-user. The pressure sensor device used in the clinical investigation is classified as laboratory equipment.
The raw data comprising volume over time will be used to define residual volumes, and flow stops, in accordance with VV-0358259.An overview of the different scales of hematuria and the translation between, are tabulated below in Table .

Table 6-1 Scales of haematuria measured with a Siemens dip stix

Negative	Negative	0 Eryt/µL	Negative
Trace	10 +/- (non-haemolysed)	10 Eryt/µL	Negative
Moderate	80 2+ (non-haemolysed)	80 Eryt/µL	Positive
Hemolyzed Trace	10 +/- (haemolysed)	10 Eryt/µL	Negative
Small/+	25 1+ (haemolysed)	25 Eryt/µL	Positive
Moderate/++	80 2+ (haemolysed)	80 Eryt/µL	Positive
Large/+++	200 3+ (haemolysed)	200 Eryt/µL	Positive

Table 6-2 Scales of leucocyturia measured with a Siemens dip stix

Negative 0 Leu/µL	15 Leu/µL1+	70 Leu/µL 2+	125 Leu/µL 3+	500 Leu/µL 4+

Take into account tracing time is 120 sec

Table 6-3 Scales of gravity measured with a Siemens dip stix

1.000	1.005	1.010	1.015	1.020	1.025	1.030

Take into account tracing time is 45 sec

6.6 Randomisation Procedure

All subjects that have given informed consent and meet the inclusion and exclusion criteria will be randomised to one of two treatment sequences. Both sequences examine the non-CE marked investigational device and the CE-marked comparator device. The two sequences are:

- First sequence: The non-CE marked investigational device, then the CE marked comparator investigational devices.

- Second sequence: The CE marked comparator investigational device, then the non-CE marked investigational device.

Randomisation will be centralized using Medidata RAVE, see section 12.1.1.

6.7 Total expected duration of the clinical investigation

The dates below are approximate, and no subjects will be enrolled before all required approvals have been obtained. If changes are required, applicable EC and regulatory authorities will be notified.

First patient in (FPI)	August 2022
Last patient in (LPI)	October 2022
Last patient out (LPO)	December 2022
Database lock (DBL)	January 2023

7 Clinical Investigation population

The clinical investigation will be conducted in 72 subjects included in 8-11 clinical investigational sites in up to 4 countries. The aim is to have equal number of subjects included in each of the four participating countries. The study population should aim towards a population distribution of 40-60% between users with neurological bladder dysfunction and non-neurological bladder dysfunction, and also an aim to have a 50/50 split between SpeediCath Flex and Vapro users.

7.1 Eligibility criteria

To be included in the investigation, the subjects must comply with the selection criteria described below.

7.1.1 Inclusion criteria

For a patient to be eligible, all inclusion criteria must be answered “yes”:

Inclusion criteria	Justification for inclusion criteria
1. **Is Male**	Intended patient population of investigational and comparator devices.
2. **Is at least 18 years of age and has full legal capacity**	Intended patient population of investigational and comparator devices. To meet Helsinki Declaration.
3. **Has given written informed consent**	To ensure that the subject has been given written and oral information regarding the investigation and know enough about the investigation to decide on participation. To ensure voluntariness and that Helsinki Declaration is met.
4. **Has signed letter of authority (only DK)**	Letter of Authority is a demand from Danish Medicines Authorities.
5. **Has used clean intermittent self-catheterisation (CISC) for at least the last 3 months**	To ensure standardisation of handling/training in intermittent catheters.
6. **Has used intermittent catheterisation as the only bladder emptying method for at least the last 3 months**	To ensure standardisation of handling/training in intermittent catheters.
7. **Self-catheterise using Coloplast SpeediCath Flex or Hollister VaPro catheters*, CH12 or CH14, for at least 3 months prior to inclusion**	To ensure standardisation of handling/training in the use of single-use hydrophilic sleeved soft/flexible intermittent catheters. The chosen brands/type are representative of this kind of catheters and estimated to correspond to the largest market shares in the countries where the study will be conducted.
8. **Is able (assessed by investigator) and willing to adhere to a 2-month study period**	To ensure sufficient data for successful completion of the study.

* VaPro, VaPro Pocket, VaPro Plus or VaPro Plus Pocket (all VaPros in sizes 20 or 40 cm)

7.1.2 Exclusion criteria

For an eligible patient, all exclusion criteria must be answered “no”:

Exclusion criteria	Justification for exclusion criteria
1. **Is participating in any other clinical study during this investigation**	To eliminate uncertainty whether any Adverse Events (AE’s) or Serious Adverse Events (SAE’s) occurring during the investigation relate to use of the herein tested devices. Also, to eliminate unintentional effect from other devices/medicines on the investigation’s data.
2. **Has previous participated in this study**	
3. **Has symptoms of urinary tract infection as judged by the investigator (rescheduling allowed within recruitment period for LPI)**	To ensure subject safety and integrity of results.
4. **Is an individual with history, suspected or showing signs of producing urine with excessive amount of mucus or large/clustered sediments or debris**	To ensure subject safety and integrity of results.
5. **Has any known allergies towards ingredients in the investigational device**	To ensure subject safety and integrity of results.

7.2 Recruitment, enrolment and inclusion

7.2.1 Definition of recruitment, enrolment, inclusion and completer

Recruitment: Active efforts by investigators to identify subjects who may be suitable for enrolment into a clinical trial. Subjects are selected based on the protocol's inclusion and exclusion criteria during the clinical trial recruitment period.

Enrolment: The process of registering or entering a subject into a clinical trial. Signing of the Informed Consent Form. Once a subject has been enrolled, the participant would then adhere to the clinical trial protocol.

Inclusion: When an enrolled subject fulfils in- and exclusion criteria and can be randomised. A subject included in the study, that – for some reason – decides to withdraw his participation, can be replaced.

Completer*:* A subject has completed the study if the subject has been enrolled and randomised and have completed treatment period 1 and 2 per protocol and have attended to the visits according to the protocol.

7.2.2 Recruitment process

The recruitment of potential subjects will commence only once authorisation has been received from the Regulatory Authorities (if applicable) and respective EC approval. Recruitment will occur through competitive enrolment in four countries: United Kingdom, Germany, France, and Denmark, but with the aim to have an even split between countries. The recruitment period from first subject enrolled to last subject enrolled is expected to be approximately 10 weeks.

When a potential subject contacts the investigator or delegated study personnel, the investigator or delegated study personnel will give a short introduction to the investigation and go over the inclusion and exclusion criteria. If the subjects are eligible and still are interested in participating in the study an information meeting is arranged and the written subject information and a writing on the subjects' rights in research projects within health sciences will be sent to the subjects to ensure that they are given the opportunity to read about the investigation before the meeting.

7.2.3 Hospital records

The recruitment method will be through subject records kept at the investigational site by the investigator or by use of the recruitment company Trialbee.

Trialbee send out general campaigns via online social media asking users of Coloplast products to sign up at the Coloplast consumer database if they are interested in being contacted for user-interviews or clinical trial participation. If interested in clinical trial and they use a catheter Trialbee contacts the user investigating whether the user match CP334. This is done by use of a study specific Nurse Script.

When the investigator has identified a potential subject from either own subject pool or has been provided a list of potential eligible subject via Trialbee platform, the investigator will contact the subject by sending them, by mail or e-mail, the written subject information, and a piece on the subjects' rights in research projects within health sciences, which they are encouraged to read. If the subject is interested in participating, he is encouraged to contact the site and an information meeting is arranged. Follow-up by phone will be done by the site (Informed consent process, section 17 and clinical investigation-related procedures, section 8.1).

7.2.4 Advertising

Advertisement will target local Coloplast consumer databases and online social media. The advertisement will state the contact information of relevant Principal Investigator(s) to contact or the web-address for a Coloplast 'recruitment landing page'. Recruitment company Trialbee will assist by receiving 'reply to' letters/mails and/or answering the phone from interested subjects.

7.2.5 Coloplast database

If needed, recruitment of subjects can also go through Coloplast's own subject database (intermittent catheter users) or by advertisements in e.g., local newspapers or relevant associations newspapers. The advertisement letter will include the contact information of the investigator or delegated study personnel (address, phone number and email address).

In the Coloplast database, potential subjects are identified by the following search criteria: subjects who have consented to be contacted for future clinical investigations and e.g., intermittent catheter user, male and at least 18 years of age and diagnose. The identified potential subjects will as first contact be sent the advertisement letter by mail or email. The advertisement letter includes the contact information of the investigator or delegated study personnel (address, phone number and email address).

7.3 Subject withdrawal criteria

The subject is allowed to withdraw from the investigation at any time for whatever reason without any consequences for their future treatment outside the clinical investigation. The Investigator may withdraw a subject from the investigation at any time if they judge it to be the subject's interest.

The investigator must withdraw a subject from the investigation due to:

- Noncompliance with the CIP impacting the scientific integrity of the investigation.
- If subject's safety and wellbeing is compromised by further participation.
- Subjects lost to follow-up. A subject will be considered lost to follow-up if at least three documented attempts (i.e., via certified letter) have been made to contact the subject and there is no response. If, after these attempts are made, and there is still no response, the subject will be withdrawn from the clinical investigation.

7.4 Subject replacement

Randomised subjects that for some reason withdraw from the clinical investigation can be replaced. Replacements should be discussed with Sponsor. Please also refer to section 11.8 Sample size for further information.

7.5 Subject Identification and Confidentiality

Subjects will be identified on the electronic CRF (e-CRF), paper quality of life and perception questionnaires, paper report of dipstick test, report of sensor measurements of urine and any other document transmitted to the sponsor by the principal investigator or clinical site staff, by a unique identification number.

Data entered in the e-CRF and questionnaires are confidential and will only be available to the sponsor (including sponsor delegates), members of data management teams, the statistician, members of the EC or IRB and if requested to regulatory authorities.

The principal investigator for each clinical investigation site will maintain as part of the investigational file a list identifying all subjects who entered the clinical investigation.

8 Procedures

8.1 Clinical investigation-related procedures

The total study duration for the individual subject will be approximately 9 weeks, consisting of up to four study visits and two 4-week test periods at home. Visits 0 and 1 can be performed on the same day. For visit 2 and 3, catheterisations will be performed in a hospital setting for bladder emptying assessment for the sub-group of minimum 42 subjects and collection of urine samples (latter only in Denmark). Test periods (at home) runs directly following visit 1 and 2 whereas visit 3 will terminate the study.

The visit window for all visits is +/- 3 days.

8.2 Pre-screening

Pre-screening is the phase where activities are done before obtaining informed consent (i.e., before enrolment). During pre-screening, the subject will receive the informed consent form and be able to have sufficient time to read it and ask questions before consenting to participate in this clinical study.

8.3 Visit 0 (V0) - Screening and inclusion:

Informed consent (and letter of authority – for DK only) is obtained before any study-related activities are initiated, including activities to determine the suitability for the study, recording baseline information (incl. the subjects regular catheterisation position), medical history and randomisation.

8.4 Visit 1 (V1) – Baseline and introduction to T1:

- Introduction to 1st randomly assigned device, including Instruction for use (IFU).
- Self-catheterization (with 1st randomly assigned device) followed by dipstick-test for haematuria, leukocyturia and specific gravity.
- DK only: Urine from the catheterisation will be collected for laboratory analysis on biomarkers (baseline).
- Instruction in recording results from stix of urine the last two weeks of T1

8.5 Test Period 1 (T1)

The four weeks of home-use with the first randomly assigned device according to an individual usage regime, include a 2-week run-in phase, followed by another 2 weeks of daily dipstick-test for haematuria, once daily after the first catheterisation in the morning. Result from dipstick should be recorded every day.

Follow-up/start dipstick-call: The nurse will call the subject when it is time to start the daily dipstick-testing.

8.6 Visit 2 (V2) – Catheterisation, follow-up and introduction to Test Period 2 (T2)

NB! To the extent possible, the subject should not have changed their medication the last 24 hours before V2.

- Assessment on user perception of catheter use and quality of life for Test Period 1. Study nurses to ensure the test subjects fill out the relevant questionnaires at the visit.
- Subgroup: Two catheterisations with the device used in T1 will be performed i.e., one by a healthcare professional and one by the user. Both followed by dipstick-test for haematuria, leukocyturia and specific gravity. All catheterisations will be performed in the same body position at all visits.
- Subgroup: Intake of fluid and waiting in the waiting room to ensure there is urine in the bladder before the second catheterisation.
- Subgroup: Assessments pertaining to performance will be recorded, including pressure measurements. This will be done immediately after each catheterisation.
- Subgroup: Three repeated measurements of residual volume will be measured with BladderScan i10 after each catheterisation is completed.
- Subgroup: After self-catheterisation, subjects are asked to assess any level of discomfort during catheter insertion, during emptying of bladder, at the end of emptying and at withdrawal of catheter (evaluated by VAS score). VAS scores are asked to be rated immediately after withdrawal of catheter.
- Dipstick-test for haematuria, leukocyturia and specific gravity after each catheterisation.
- Subgroup: Urine from both catheterisations will be collected for laboratory analysis on biomarkers (DK only).
- Introduction to 2nd randomly assigned device, including IFU.
- Instruction in recording results from stix of urine the last two weeks of T2

8.7 Test period 2 (T2)

Four weeks of home-use of the second randomly assigned device according to individual usage regime, including a 2-week run-in phase, followed by another 2 weeks with dipstick-test for haematuria, once daily at the first catheterisation in the morning. Result from dipstick should be recorded every day.

Follow-up/start dipstick-call: The nurse will call the subject when it is time to start the daily dipstick-testing.

8.8 Visit 3 (V3) – Catheterisation, follow-up and termination

NB! The subject should not have changed their medication the last 24 hours before V3.

- Assessment on user perception of catheter use and quality of life for Test Period 2. Study nurses to ensure the test subjects fill out the relevant questionnaires at the visit.
- Subgroup: Two catheterisations with the device used in T2 will be performed i.e., one by a healthcare professional and one by the user. Both followed by dipstick-test for haematuria, leukocyturia and specific gravity. All catheterisations will be performed in the same body position at all visits.
- Subgroup: Intake of fluid and waiting in the waiting room to ensure there is urine in the bladder before the second catheterisation.
- Subgroup: Assessments pertaining to performance will be recorded, including pressure measurements. This will be done immediately after each catheterisation.
- Subgroup: Three repeated measurements of residual volume will be measured with BladderScan i10 after each catheterisation is completed.
- Subgroup: After self-catheterisation, subjects are asked to assess any level of discomfort during catheter insertion, during emptying of bladder, at the end of emptying and at withdrawal of catheter (evaluated by VAS score). VAS scores are asked to be rated immediately after withdrawal of catheter.
- Dipstick-test for haematuria, leukocyturia and specific gravity after each catheterisation.
- Subgroup: Urine from both catheterisations will be collected for laboratory analysis on biomarkers (DK only).

- Termination of the study.
- Site staff to inform subject of return to SoC use of catheter after completion of study.

8.9 Unscheduled visit/call

If it, for any reason, is necessary for the subject to come into the clinic, an additional visit may be scheduled. The unscheduled visit form in the eCRF should be completed. The following data should be recorded: Visit date, reason for unscheduled visit, stix of urine for haematuria, and leukocytopenia, medical history, and concomitant to be updated. Adverse Event form to be completed if relevant.

If an unscheduled call is needed the following data should be recorded: call date, relevant standard forms (Device Deficiency Form, Protocol Deviation Form, Adverse Event Form, Concomitant Medication Form).

8.10 Safety Follow up

Adverse events and device deficiencies will be assessed at all visits, planned and unplanned. Subjects are followed through termination of the investigation (Visit 3). Any ongoing ADEs or SADEs at study termination will be followed until resolution. All subjects are encouraged to contact the Principal Investigator, or designee, if they experience problems that they believe are related to their investigational device or participation. This is to ensure that any device-related events are documented and to safeguard the subjects' health.

8.11 Flow-chart

Time point & Assessment	V0	V1	Test period 1 T1				Visit 2 V2											Test period 2 T2				Visit 3 V3												Termination visit
							HCP catheterisation*****						Self catheterisation									HCP catheterisation*****						Self catheterisation						
			Run-in		Steady State		Pre	During				Post	Pre	During				Post	Run-in		Steady state		Pre	During				Post	Pre	During				Post	
			week 1	week 2	week 3 (7 days)	week 4 (7 days)		insertion	1st flow stop	urination	withdrawal			insertion	1st flow stop*****	urination	Withdrawal		week 1	week 2	week 3 (7 days)	week 4 (7 days)		insertion	1st flow stop	urination	withdrawal			insertion	1st flow stop*****	urination	withdrawal		
USER RELATED INFO/ASSESSMENTS																																		
Informed consent process	•																																	
In/exclusion criteria	•																																	
Demography	•																																	
Concomitant illness/Medical history	•																																	
Randomisation	•																																	
Introduction to home-use		•															•																	
Concomitant medication*	•	•	•	•	•	•	•											•	•	•	•	•											•	
Adverse events		•	•	•	•	•	•											•	•	•	•	•											•	
ASSESSMENTS PERTAINING TO ENDPOINTS																																		
Urine volume (scale)*****									•			•			•		•							•			•				•			•	

Time point & Assessment	V0	V1	Test period 1 T1				Visit 2 V2											Test period 2 T2				Visit 3 V3											Termination visit
							HCP catheterisation*****						Self catheterisation									HCP catheterisation*****						Self catheterisation					
			Run-in		Steady State		Pre	During				Post	Pre	During				Post	Run-in		Steady state		Pre	During				Post	Pre	During				Post	
			week 1	week 2	week 3 (7 days)	week 4 (7 days)		insertion	1st flow stop	urination	withdrawal			insertion	1st flow stop*****	urination	Withdrawal		week 1	week 2	week 3 (7 days)	week 4 (7 days)		insertion	1st flow stop	urination	withdrawal			insertion	1st flow stop*****	urination	withdrawal		
Self-catheterisation at site**		•												•																•				
HCP catheterisation at site**/****'								•																•										
Pressure sensor measuring while catheterising'*****								•						•										•						•				
Residual urine measured by US***/****'												•						•									•							•
HCP call to remind of dip-stix at home				•															•															
Haematuria (dip stick) assessed on an ordinal scale		•			•	•						•						•		•	•						•							•
Leukocyturia (dip stick)		•										•						•									•							•
Specific gravity (dip stick)		•										•						•									•							•
Discomfort VAS*****		•												•																•				

Time point & Assessment	V0	V1	Test period 1 T1				Visit 2 V2											Test period 2 T2				Visit 3 V3												Termination visit
							HCP catheterisation*****						Self catheterisation									HCP catheterisation*****						Self catheterisation						
			Run-in		Steady State		Pre	During				Post	Pre	During				Post	Run-in		Steady state		Pre	During				Post	Pre	During				Post	
			week 1	week 2	week 3 (7 days)	week 4 (7 days)		insertion	1st flow stop	urination	withdrawal			insertion	1st flow stop*****	urination	Withdrawal		week 1	week 2	week 3 (7 days)	week 4 (7 days)		insertion	1st flow stop	urination	withdrawal			insertion	1st flow stop*****	urination	withdrawal		
Qualiveen questionnaire (Appendix)							•															•												
Perception questionnaire (Appendix)							•															•												
OTHER ASSESSMENTS: DANISH SITE ONLY																																		
Biomarkers****		•															•																•	
STUDY MATERIAL																																		
Dispensing of catheters for home-use + IFU (only investigational device)		•															•																	
Dipstix for home use		•															•																	
Catheter accountability																	•																•	
Study termination																																	•	•

*Remind subject – not to change medication 24 hours before visit
**Remember to adhere to the same position throughout the investigation
***3 consecutive measurements of residual urine (bladder scan)
****Biomarkers to be analysed – see section 6.2.5:
***** Only for the 42 subjects evaluating bladder emptying residual volume and flow-stop episodes

8.12 Concomitant Medications

Concomitant medication taken from the time of consent through the study until termination will be registered in the eCRF in the concomitant medication section.
To the extent possible – the subjects should not have changed their medication the last 24 hours before test visit 1-3. Any changes in medicine should be recorded under concomitant medication.

8.12.1 Activities performed by sponsor representatives

Sponsor (Clinical Manager or a representative hereof) is responsible for:

- Training of the investigator and investigational personnel in the informed consent procedure, clinical investigational plan, investigational procedures, how to use the investigational device s, how to perform accountability of devices, completion of the CRF, how to report possible safety issues and training in ISO 14155. All training will be documented
- Support during the recruitment process, the conduct, and the completion of the investigation
- Training in use of the equipment to be used for pressure sensor measurements
- For DK sites only: Transportation of collected urine from site to Coloplast
- General support during the duration of the investigation
- Monitoring according to monitoring plan

9 Risk – benefit analysis and ethical considerations

9.1 Risk-benefit analysis of the investigational device

A risk analysis according to ISO 14971 Application of risk management to medical devices has been conducted. Risks have been proven minimized or eliminated through appropriate design control, confirmed by pre-clinical bench and laboratory testing.

Remaining risks needing further studies in humans can be described as follows:

A number of risks connected to use of the test device have been identified in the Product Risk Assessment. All risks will be mitigated before release of devices for the clinical investigation. The risk management process has been performed in accordance with the requirements stated in ISO 14971:2012 and in accordance with internal Coloplast procedures, including design verification, validated test methods, risk analysis and completion of a biological evaluation report for the test device.

The following risks will be mitigated by actions during the clinical investigation.

- Urinary tract infection. Frequent test of urine will be done both in clinic setting and home setting. In clinic setting urine stix will be evaluated by HCP and in home setting the subject is instructed in contacting the clinical HCP in case the subject is in doubt if they have a UTI.
- Mild pain or bleeding. If seen, this will be discussed with HCP. Haematuria will be measured frequently in the urine during the study.

To mitigate and reduce the risks, the subjects will be trained, according to the IFU, in use of the device.

The investigation is conducted in accordance with current law and applicable standards. Please refer to section 16, Statement of compliance. The rights, safety and well-being of human subjects shall prevail over the interest of science of society.

9.2 Risk-benefit for subjects participating in the clinical investigation

The investigation is conducted in accordance with current law and applicable standards, see section 16. Statement of Compliance. The rights, safety and well-being of human subjects shall prevail over the interest of science of society.

The catheterisation of subjects, with both investigational device and the comparator will be performed by experienced urology nurses at sites with many years of experience in conducting IC and with previous experience in working with clinical investigations.

Risks have been proven minimized or eliminated through appropriate Risk control measures, confirmed by pre-clinical bench, laboratory, and biological safety evaluations. Completed pre-clinical and clinical studies on the new catheter concept did not reveal any additional risks associated with the investigational catheter [Coloplast A/S 2021d]. Risks associated with the investigation may be discomfort or stinging in the urethra during the catheterisation and additional risk of micro-trauma and haematuria after catheterisation, which is expected to heal within 1-3 days. Hence, the risks are considered equal to the use of intermittent catheters already on the market.
To mitigate and reduce these risks, subjects will be trained, according to the IFU, in correct handling and catheterisation of the investigator and comparator device. The investigational setting is not expected to result in increased frequency or severity of the known risks associated with urethral catheterisation.

There are no direct benefits for the subjects involved; but, by participating in this investigation, the subjects will contribute with important information for developing improved solutions for urinary IC that in turn may benefit individuals who are dependent on catheters for emptying their bladder. The subjects will be compensated for the time spent (see section 18.2).

For further information on Adverse Events for this study please refer to section 19.

9.3 Risk Analysis for the conduct of the clinical investigation

A risk assessment of the clinical investigation will be conducted initially prior to the first subject enrolment and periodically re-assessed based on any new risks identified through the process. This assessment will be completed throughout the duration of the investigation, as defined by the study team. A risk-based monitoring strategy may be implemented including on-site remote, and central monitoring. Details of the strategy are defined in the monitoring plan.

9.4 Delegation of responsibility

Before initiation of the clinical investigation, sponsor must be provided with key personnel signed and dated curriculum vitae (not more than 2 years old) to verify their qualifications. Key site personnel are those, who treat or evaluate subject data in the clinical investigation. Also, the sponsor will ensure that all site personnel are trained in the investigation procedures, how to complete the CRFs, procedure for reporting an adverse event or serious adverse event (how, when, to whom), and who to contact in case of emergency related to the investigational device.

10 Monitoring and visit Plan

The sponsor is responsible for ensuring appropriate monitoring of the clinical investigation activities. A study-specific monitoring plan has been developed and includes details regarding the monitoring strategy (i.e., on-site, remote, and centralized).

In some cases, the monitoring of this clinical investigation has been delegated by the sponsor to a clinical research organisation (CRO). The monitors will be the primary contact for the Principal Investigator and clinical investigation site personnel.

Monitoring activities are mandatory as per good clinical practice; however, the extent and depth of these activities depend on the criticality of the clinical investigation, speed of enrolment, the experience of the clinical investigation site personnel in carrying out clinical investigations and specific study designs.

The monitoring process is briefly described below and is described in more detail in the Monitoring Plan.

The data collected throughout the investigation and the conduct of the investigation, will be monitored according to the monitoring plan to ensure, and verify, that the rights and well-being of the subjects are protected, that the reported data are accurate, complete, and verifiable from source documents, and that the

conduct of the investigation complies with the approved CIP, subsequent amendment(s) (if any), ISO14155 and the applicable regulatory requirement(s).

The monitoring will be conducted periodically at all sites by qualified personnel.

The investigator must be available for and agrees to cooperate with Coloplast Clinical Managers (CM) and/or the Clinical Research Associates (CRA) during their visits and ensure that they have direct access to all documents required, including direct access to the subjects' files, to ensure thorough monitoring.

The investigation will be subject to internal audits if relevant. All monitoring visits and possible audits will be followed by internal reports and corrective actions, if needed. Follow-up letters will be forwarded to sites after all visits and any findings should be addressed by the investigator or designee.

To ensure proper conduct of the investigation the following visits on site or as remote visits will be performed during the investigation:

- Site selection visit
- Site initiation visit
- Periodic monitoring visits
- Close out visit

10.1 Site Selection visit

Depending on the prospective clinical investigation site's experience with the specific investigational device, an on-site qualification or site selection visit shall be performed during which the feasibility of the clinical investigation requirements will be discussed and common agreement between sponsor and principal investigator shall be reached. This visit may also be replaced by one or more phone calls, i.e., if the Principal Investigator is known to the sponsor.

10.2 Site Initiation visit

Before initiation of the clinical investigation, sponsor must be provided with key personnel signed and dated curriculum vitae (not more than two years old) and documentation of current qualifying training (i.e., ISO14155) to verify their qualifications.

All clinical investigation sites will get an initiation visit during which full training on all aspects of the clinical investigation will be provided. This visit can be done on-site or remotely.

Training in use of equipment used for measuring primary endpoint will be performed on site.

10.3 Site Monitoring visit(s)

The site dedicated monitor is to ensure adherence to the clinical investigation plan, accurate data recording on the eCRFs and to monitor recruitment rates and adherence to follow-up schedules. The Principal Investigator shall permit and assist the monitor to carry out verification of completed eCRFs against data in the source documents.

The Principal Investigator can delegate tasks to his/her personnel, however the role and time period of involvement for each clinical site personnel must be documented on the delegation log. Training for all delegated site personnel will be documented on the training log before any involvement with the clinical investigation.

The monitor shall inform the sponsor about any problems relating to facilities, technical equipment, or medical staff at the clinical investigation site. During the clinical investigation, monitors shall check that appropriate written informed consents have been obtained. The monitor shall also be responsible for notifying such deficiencies in writing to the Principal Investigator and convene with the clinical investigation site personnel appropriate and timely corrective actions.

The sponsor, or delegate, will provide clinical monitoring, including review of eCRF with verification to the source documentation, as defined in the monitoring plan. The monitor shall make written reports to the sponsor, after each visit and provide written action items if any, to the Principal Investigator or clinical investigation site personnel.

Periodic monitoring visits (remote or on-site) will be performed as soon as reasonable possible, after the site has enrolled the first subject in the investigation. A final monitoring visit will be performed after all subjects on site have completed the investigation.

10.4 Remote monitoring

Remote (source data verification) and/or centralized (data review) monitoring is carried out by sponsor personnel or representatives (e.g., data management personnel, statisticians, or clinical monitors) at a location other than the site(s) at which the clinical investigation is being conducted (evaluation without visiting the investigation site). Remote monitoring processes can provide many of the capabilities of on-site monitoring as well as additional capabilities.

In addition to onsite monitoring visits, remote monitoring of the data entered in the e-CRF system could be used to achieve the following:

- Conduct activities such as: standard checks of range, consistency, and completeness of data and checks for unusual distribution of data, such as too little variance)
- Special attention will be given in case of frequent data anomalies or errors, protocol deviations or excessive dropouts.
- Augment on-site monitoring by performing monitoring activities that can only be accomplished using centralized processes (e.g., statistical analyses to identify data trends not easily detected by on-site monitoring)
- Monitor data quality through routine review of submitted data in real-time to identify missing data, inconsistent data, data outliers, and potential protocol deviations that may be indicative of systemic and/or significant errors in data collection and reporting at the site
- Verify source data remotely, provided that both source data and CRFs can be accessed remotely
- Conduct aggregate statistical analyses of study data to identify subject data that are outliers relative to others and to evaluate individual subject data for plausibility and completeness
- Conduct analyses of site characteristics, performance metrics (e.g., high screen failure rates, high frequency of eligibility deviations, and delays in reporting data), and clinical data to identify early on corrective actions needed for characteristics correlated with poor performance or noncompliance

10.5 Source data verification

Source data is all information in original records, certified copies of original records of clinical findings, observations, or other activities in the clinical investigation, necessary for the reconstruction and evaluation of the clinical investigation. This includes source data initially recorded in an electronic format.

All documents and data related to the clinical investigation handled by site personnel, shall be produced and maintained in a way that assures reliability, integrity, control and traceability, and shall be appropriately stored to provide a complete history.

The Principal Investigator shall assure the accuracy, attribution, completeness, legibility, and timeliness of the data reported to the sponsor in the eCRFs and in all required reports. All printed copies of electronic source documents shall be certified, as indicated by a dated signature by the investigational site personnel at the time the document is printed. Special requirements should be applied to the capture, review, and retention of electronic source data, to ensure reliability, quality, integrity and traceability.

The data reported in the eCRFs shall be derived from source documents and be consistent with these source documents, and any discrepancies shall be explained in writing. The eCRF can serve as the source document and this must be documented on the Source Data Specification Form. The Source Data

Specification Form must be completed at the initiation visit detailing the location of the source data for each data point agreed upon by the principal investigator.

11 Statistical considerations

11.1 Statistical design, method, and analytical procedures

The primary objective will be evaluated by analysing the two primary endpoints and the secondary objective will be evaluated by analysing the secondary endpoints. Supportive and exploratory endpoints will support and further evaluate the primary objective.

Baseline assessments and endpoints will be reported by descriptive statistics and/or listed. Summaries will be presented by device i.e., investigational or comparator device and if relevant, by other grouping variables.

Descriptive statistics for continuous variables are presented with N, Mean, SD (standard deviation), Median, Min and Max, where N denotes the number of subjects contributing with non-missing data. For discrete variables, descriptive statistics are presented with N and percentage, where percentage is based on the total number of subjects/observations with non-missing data.

All statistical analysis will be performed with SAS (version 6.4/Enterprise Guide version 7.1).

11.2 Definition of analysis populations

Screening Failures (SF), Intention to Treat (ITT), Full Analysis Set (FAS), Safety and Per Protocol (PP) analysis set will be defined at a formal data review meeting prior to database lock. As a minimum, the data manager, the clinical manager, and the statistician will be involved in the classification of subjects.

Subjects not adhering to inclusion and/or exclusion criteria are considered screening failures (SF) and are not randomised.

The Safety population will constitute all subjects enrolled i.e., subjects who have given informed consent.

The ITT population will constitute all randomised subjects.

The full analysis set is a modified ITT population i.e., a sub-population of the ITT population, and will constitute all randomised subjects, who have been exposed to at least one device, with at least one endpoint recorded (data non-missing).

The PP is a sub-population of the full analysis set where all subjects have received treatment as per protocol.

Individual endpoints/data points may be excluded from the analysis, even though the corresponding subject belongs to any of the pre-defined populations. Exclusion of subjects or data points must be documented.

All statistical analysis and test of hypothesis will be based on the full analysis set, and in addition, Primary and Secondary endpoints will also be analysed in the PP population, if the PP population differs from the full analysis set. whereas adverse events and device deficiencies will be assessed in the safety population.

11.3 Multiplicity control and adjustment of error probabilities

The family-wise Type I error rate will be controlled in a hierarchical fashion in support of demonstrating superiority of the investigational device.

The primary endpoints will be evaluated in a fixed sequence, where the first null-hypothesis must be rejected at a 5% significance level (alpha 0.05) before proceeding with the next.

11.4 Analysis of the primary endpoint

- Residual volume at first flow-stop, will be analysed in a general linear mixed model with subject included as a random component. Evidence of superior effect will be concluded, if the 95% confidence interval of the difference between comparator and investigational device, do not include zero.

- Number of flow-stop episodes will be analysed, in a generalized linier mixed model, with subject included as a random component. Evidence of superior effect will be concluded, if the lower 95% confidence limit of the risk ratio between comparator and investigational device, is more than 1.

The models will include following fixed effects.

- Visit (visit 2 and 3 of catheterisation)
- Device (comparator and investigational device)

11.5 Analysis of the secondary endpoints

- Red blood cell concentration will be analysed in a general linear mixed model with repeated measurements where subject and subject*device are included as random components. Evidence of superior effect will be concluded, if the 95% confidence interval of the difference between comparator and investigational device, do not include zero.

- Frequency of positive haematuria events will be analysed, in a generalized linier mixed model with repeated measurements, where subject and subject*device will be included as random components. Evidence of superior effect will be concluded, if the lower 95% confidence limit of the odds ratio between comparator and investigational device, is more than 1.

The models will include following fixed effects.

- Visit (visit 2 and 3 of catheterisation)
- Device (comparator and investigational device)

11.6 Analysis of supportive and explorative endpoints

Assessments and Endpoints pertaining to

- Residual volume at 1st flow-stop (RV1) (self-catheterisation)
- Pressure measurement at 1st flow-stop (self-catheterisation)
- Average residual volume post catheterisation
- Discomfort at insertion, emptying and withdrawal
- QoL Index score (Qualiveen questionnaire)

Will be analysed by a general linear mixed model identical to the model specified for the primary endpoint.

Endpoints pertaining to

- Number of flow-stops (self-catheterisation)
- Perception questions evaluated on a 5-point ordinal scale

Will be analysed by a generalized linear mixed model identical to the model specified for the primary endpoint.

11.7 Analysis of safety data

Adverse events will be listed and/or summarized. Device deficiencies and concomitant medications will be listed.

11.8 Sample size

Input for the sample size calculations i.e., frequencies, rates, means and standard deviations are based on three exploratory studies CP322, CP323 and CP324. The studies investigated earlier prototypes of the micro-hole zone catheter with identical or similar endpoints in populations of both IC users and healthy volunteers.

A sample size for the primary endpoint of residual urine at 1st flow stop (RV1) is judged to be accommodated by 30 subjects with a power above 90%, assuming a difference of 40 mL, a $sd_{comparator}$ of 50 mL and a sd_{active} of 10 mL. (please see table 11-1). Taken into consideration a discontinuation of 20%, the endpoint of RV1 is sufficiently supported by randomising at least 36 subjects.

For primary endpoint of flow stop episodes a sufficient sample size is judged to be accommodated by 35 subjects with a power above 90%, assuming a difference of 1 flow stop with a $\lambda_{comparator}$ of 2 flow stop, and a λ_{active} of 1 flow stop (please see table 11-2). Taken into consideration a discontinuation of 20%, the endpoint of RV1 is sufficiently supported by randomising at least 42 subjects.

Aiming for an acceptably narrow 95% confidence interval, for the difference in frequency of positive haematuria events, sufficient inference is judged to be accommodated with 60 subjects completing the study (please see table 11-3). Taken into consideration a discontinuation of 20%, the aim is to randomise at least 72 subjects.

72 subjects should at least be randomised in support of the secondary endpoint of positive haematuria frequency and a sub-set of subjects, at least 42, should be randomised in support of the primary endpoints RV1 and number of flow stop episodes.

Table 11-1 Sample size calculation of Residual urine at 1st flow stop in a cross-over design, solving for varying power and number of subjects, assuming no within subject correlation as a worst-case approach, using proc Power in SAS.

μ (sd) comparator	μ (sd) active	Alpha	Power	Sample size
50 (90)	10 (15)	0.05	86.0 %	25
50 (90)	10 (15)	0.05	90.0 %	28
50 (90)	10 (15)	0.05	91.6 %	30

Table 11-2 Sample size simulation of Flow stop events in a cross-over design, solving for varying power and number of subjects, assuming no within subject correlation as a worst-case approach, using a generalised linear mixed model with proc Glimmix in SAS.

λ comparator	λ active	Alpha	Power	Sample size
2	1	0.05	81.2 %	25
2	1	0.05	88.0 %	30
2	1	0.05	92.2 %	35

Table 11-3 Sample size simulation of the positive haematuria frequency in a cross-over design, assuming 10 repeated measurements in each period and a within subject correlation of 50%, solving for varying frequencies and power, with a fixed sample size of 60 subjects, using a generalised linear mixed model with proc Glimmix in SAS.

P comparator	P active	Alpha	Power	Sample size
20 %	14 %	0.05	65.0 %	60
20 %	13 %	0.05	90.0 %	60
20 %	12 %	0.05	98.0 %	60

If the discontinuation exceeds 20% i.e., the number of subjects completing the study, is likely to be less than 60 subjects, additional subjects will be included (subjects replaced), to ensure at least 60 subjects completing and thereby maintain sufficient power in the study.

11.9 Level of significance and power

A significance level of alpha 0.05 (2-sided) will be applied.

The power for concluding superiority of the investigational device is at least 90% or higher.

11.10 Pass/fail criteria

To demonstrate superiority of the investigational device, the null hypothesis of the primary endpoints must be rejected, at a 5% significance (alpha 0.05).

The pass criteria for the study are based on the results from analysing the two primary endpoints in a hierarchical fashion: rejecting the null-hypothesis on the first endpoint (Residual urine at first flow-stop) before continuing to the second (Number of flow-stop episodes).

12 Data management

12.1 Data collection and data management

12.1.1 Data Collection in the clinical investigation

Data management and statistical analyses are carried out by Medical Affairs, Coloplast A/S.

Data will be collected through an electronic data capturing (EDC) system on electronic Case Report Forms (eCRF), a secure, internet-based case report form. This system will be used to record all subject information collected in the investigation for secure data tracking and centralised data monitoring (“remote monitoring”) done by monitors, as defined in the monitoring plan.

The EDC system used is Rave EDC, version 20121.1.4, delivered by Medidata Solutions Inc. The system is designed to be compliant with the FDA requirements of 21 CFR part 11. It is a validated data management system allowing only qualified and trained personnel to enter the system. The system has full audit trail and electronic signature.

The sponsor will be responsible for training the investigator or delegate, in completion of the eCRF.

Principal Investigator, or delegate, at the clinical site will perform primary data collection directly into the eCRF or drawn from source-document (i.e. paper CRF, medical records etc. according to the Source Data

Specification Form) reviews. The eCRF will be completed on a continuous basis starting from the point of enrolling the subject to final follow up.

The eCRF will be completed by the investigator, or delegate, who have signed the Site Personnel Signature and Delegation List and Clinical Investigation Training Log. It will be the responsibility of the investigator to ensure that all measurements and observations are correctly noted in the eCRF.

All assessments and observations throughout the investigation for each subject must be carefully recorded in an eCRF during the visit or immediately after. The eCRF makes it possible to enter data right away when they are obtained. This is the preferred way of collecting data. In case this is not possible the data should be entered no later than 7 days after the visit / procedure.

Subject reported outcomes (Perception questionnaire, the quality-of-life questionnaire (Qualiveen), VAS scale and dipstick results during the two weeks of home use) will be completed by the subject in a paper CRF and entered into the eCRF by site personnel. After completion of the VAS scale by subject, the site personnel will measure the VAS-scale and enter the measurement in the eCRF.

Data from urine analysis will be batch uploaded into the EDC system.

Data derived from the catheterisation profile will be batch uploaded into the EDC system.

Raw data from the scale/balance and from the pressure sensor are stored in the electric boxes and copied on USB sticks. The USB sticks are sent to Coloplast A/S via courier. Raw data from either the USB sticks or the electric box are then analysed by two specialists independently.

A calibration/comparison is then performed between the two specialists and an excel sheet is made combining the relevant data. The excel sheet is thereby uploaded to an allocated SharePoint.

Adverse events should be registered following the timelines described in the Adverse Event section.

In the unforeseen situation, where site cannot establish connection to the EDC system a paper CRF (pCRF) has been printed and supplied by sponsor.

The investigator will keep a separate list of the subjects' ID numbers, names and addresses in a locked room/cabinet. Only data referred to in this clinical investigation plan will be recorded in the CRFs.

12.1.2 Database Management, Queries and Quality Control

The data management system has restricted role-based access control. The principal investigator or delegate must be trained in the system prior to getting access. The training is web-based and must be completed before access to the investigation is granted. Training will be documented in the data management system. Only the principal investigator, or delegate, will be authorised to enter data in the eCRF.

The monitor, using his/her personal login information shall verify all critical data points against the source documents and issue electronic queries for the authorised clinical site personnel to respond, as defined in the monitoring plan.

The principal investigator, using his/her personal login information shall sign each eCRF.

Automated, real-time access to the data enable control on study compliance and safety assessments.

A critical quality control will be performed by the sponsor's data management team and queries issued where needed. Such queries will be reviewed by the monitor and must be resolved by the site personnel.

At the end of the study a formal data review meeting will be performed before the database will be locked.

A full audit trail ensures, that each user's (site personnel, monitor, sponsor, data manager) access to and actions in the system is tracked.

The Data Management Procedures are further described in the Data Management instructions.

12.2 Data retention

The Investigator file must be archived for a minimum period of 10 years after the final clinical investigation report has been signed.

13 Amendments to the Clinical Investigation Plan

No changes in the clinical investigation procedures shall be affected without mutual agreement between the principal investigator and the sponsor. The agreement of the changes must be documented by signing the corresponding clinical investigation plan amendments and registered in the Change Log.

All significant changes require notification to the Ethical Committee and applicable regulatory authority. Substantial changes may require approval from the Ethical Committee and applicable regulatory authority prior to implementation.

14 Deviations from the Clinical Investigation Plan

Deviations to the Clinical Investigation Plan occurs when the activities during the clinical investigation do not comply with the Ethical Committee and applicable regulatory authority approvals.

A minor deviation is defined as those that don't increase risk or decrease benefit or don't have a significant effect on the subject's rights, safety or welfare; and/or on the integrity of the data. If a deviation increases risk or decreases benefit and/or; has a significant effect on the subject's rights, safety or welfare and/or has a significant effect on the integrity of the data it is defined as a major deviation and the Investigator must inform the monitor immediately, and the Monitor will report and inform the Clinical Manager or designee immediately.

The investigator is not allowed to deviate from the Clinical Investigation Plan unless, under emergency circumstances or to protect the rights, safety, and welfare of the subject(s).

For the purposes of this investigation, any variance from the protocol is considered a deviation and is to be reported.

The site will complete a deviation eCRF form for all data-related deviations and all deviations that are **not** related to the data (for example, an untrained nurse performing study procedures) are reported by the monitor in the Periodic Monitoring Site Report and actions are addressed to the Investigator for completion.

If any deviations to the investigation plan are detected during the monitoring visit, the Monitor shall ensure the site reports all deviations in the eCRF or on the Deviation log in the Investigator File. Additionally, the monitor must report any deviation noted during the visit in the Periodic Monitoring Report.

Monitor will align with data management in each investigation, how data management will be informed about all deviations.

The following information about the deviation will be collected:

- Site ID
- Subject ID
- Date the deviation took place
- What the deviation is related to

- If the deviation affects data integrity
- If the deviation affects subject safety
- Supplementary description of the deviation
- Actions taken with regards to the deviation

15 Device Accountability

All access to the investigational devices used in the clinical investigation is controlled by storage procedures and device accountability logs as described below. The investigational devices must only be used in this clinical investigation and only according to the CIP.

Sponsor keeps a device accountability log that states the physical location of all investigational devices from shipment of investigations devices to the investigational sites until return of or disposal.

The principal investigator or an authorized designee keeps records documenting the receipt, use and return and disposal of the investigational devices, which includes:

- Subject identification
- Identification of each investigational device (batch no./serial no./unique code)
- The expiry date, if applicable
- The date(s) of use, if possible
- The date on which the investigational device was returned from the subject
- Number of devices handed out to subject

16 Statement of compliance

The clinical investigation is conducted in accordance with:

- The investigation is conducted in accordance with 'The Declaration of Helsinki', 1964, last amended at the 64th WMA General Assembly, Fortaleza, Brazil, October 2013
- MDR (EU) 2017/745
- ISO 14155:2020 "Clinical Investigation of medical devices for human subjects – Good clinical practices".
- Any applicable regional or national regulations will be specified in the country specific CIP.

16.1 Ethics committee and regulatory authorities

The CIP and/or other relevant documents are submitted to the appropriate EC(s) and regulatory authorities. This clinical investigation will not begin until the required approval from the EC and regulatory authorities have been obtained. Any amendment to the protocol will be submitted to the same EC(s) and regulatory authority.

Sponsor will notify the relevant regulatory authority and EC(s) concerned of the end of the clinical investigation.

16.2 Other relevant authorities

National requirements for submission to committees and authorities will be followed.

16.3 Data protection

As part of the investigation Coloplast A/S, Holtedam 1, 3050 Humlebaek, Denmark ("Coloplast") will collect and process the personal information the subject provides for the investigation ("subject personal data"). This

includes identification and contact information (which may be anonymised depending on the nature of the investigation) as well as information about device usage experience and your health. Coloplast will comply with the EU General Data Protection Regulation (GDPR) and the Danish act on data protection ("databeskyttelsesloven"), including in connection with transfer of data to third countries, cf. chapter V of GDPR, Coloplast will only process the subjects' personal data:

1. To conduct the investigation and carry out related research based on subject consent (primary use), cf. articles 6(1)(a) and 9(2)(a) of GDPR,
2. To comply with applicable legal obligations to e.g. ensure reliability and safety, cf. article 6(1)(c) in conjunction with article 9(1)(i) of GDPR, and
3. If separate consent is given for secondary use of subject personal data, cf. articles 6(1)(a) and 9(2)(a) of GDPR – carry out research outside the clinical protocol to improve Coloplast's devices and services, and for use in education.

Part of Coloplast's processing is carried out on third-party platforms (clinical trial databases) and certain third parties are assisting Coloplast in the processing (e.g. the investigator). Such cases will imply a transfer of your personal data to the third parties, but solely for the specified purposes and with the third parties acting on instruction from Coloplast. Data may be collected and processed across the Coloplast network, which may entail processing of personal data outside the European Economic Area. In such cases, an adequate level of protection will be ensured by the third parties being subject to the standard contractual clauses on data protection adopted by the EU or to an EU-approved certification mechanism on data protection. For further information about this please the subject can always consult Coloplast's data protection officer (details below).

Subject personal data will be kept as long as required under applicable laws and regulations. The EU Medical Device Regulation obligates Coloplast to keep the data for a period of at least ten years after the investigation is completed, or, in the event that the device is subsequently placed on the market, at least ten years after the last device has been placed on the market. Subject personal data will be deleted at the end of the mandatory retention period.

If the subject has questions or queries regarding Coloplast's handling of personal information, the subject can always contact Coloplast's Data Protection Officer at dataprotectionoffice@coloplast.com. Complaints related to Coloplast's handling of subject personal information may similarly be sent to the Data Protection Officer, and the subject is also entitled to file a complaint with the relevant supervisory authority, which in the case of Denmark is the Danish Data Protection Agency (www.datatilsynet.dk).

The subject can write to privacyrequests@coloplast.com at any time to request:

- Access to personal data
- Correction of errors in personal data or to erase personal data
- Limit what can be done with personal data
- To receive personal data in machine-readable format (data portability).
- Withdrawal of consents the subject has given Coloplast to process personal data

16.4 Indemnity

All subjects are fully covered by Coloplast A/S insurance throughout the investigation. Insurance has been signed with:

XL Insurance Company SE
Kungsgatan 5, 2nd floor
SE-111 36 Stockholm
Phone +46 8 440 89 80

16.5 Financial conditions

Coloplast A/S will compensate all investigators involved in the clinical investigation for their time and resources spent on the investigation. All financial agreements with the investigation sites involved in the clinical investigation will be specified in a sponsor investigator agreement.

17 Informed consent process

Written informed consent is obtained from all subjects participating in the investigation after thorough written and verbal information. The information is given by the investigator or his/her representative in the subjects' native non-technical language. Each subject will be fully informed about the aim of the investigation, procedures, potential risks, or inconveniences and/or expected benefits and all anticipated adverse device effects and ensure ample time is provided before deciding on participation. The subjects will be informed that their participation is voluntary and that they may leave the investigation at any time, without this having any influence on their further treatment.

The informed consent signature form includes personally dated signatures of the subject and the PI or his/her representative responsible for conducting the informed consent process. A copy will be provided to the subject.

If new information is to be given during the investigation, sponsor will inform the investigators, and the new information is given to the subjects by the investigator. If new information becomes available that can significantly affect a subject's future health and medical care that information will be provided to the subject in written form. CM is responsible for writing the information and providing the approved Subject Information and Consent Form to investigators that will further provide it to the subjects. If applicable, all affected subjects shall be asked to confirm their continuing informed consent in writing.

This procedure also applies to informed consent obtained from a subject's legal representative. The procedure cannot waive the subjects' legal rights.

18 Subject compensation

18.1 Compensation in case of injury

Device liability and No-Fault Clinical Investigation Insurance covering the duration of the clinical investigation are in place, to enable compensation in the event of an injury to a participating subject.

18.2 Compensation for participating in the clinical investigation

Subjects will be compensated with a voucher per visit, paid by Coloplast A/S with the value as described below:

	Subjects
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

This is to compensate for any inconvenience caused during the catheterisations, time used. Travel expenses will be accounted for separately. For Danish subjects, the remuneration/vouchers are taxable (B-income) and it is the responsibility of the subject to declare this to SKAT.

19 Adverse events, adverse device effects and device deficiencies

19.1 Adverse events

An adverse event is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, whether related to the investigational medical device(s) or the comparator(s), or the procedures involved. The adverse event shall be marked with the intensity mild, moderate, or severe. This could include events such as headache or dizziness.

19.2 Adverse device effect

An adverse event, which is related to the use of the investigational medical device, is an adverse device effect, and should be marked as unlikely related, possible related, probable related or with causal relationship on the adverse event form.

The definition of an adverse device effect includes any event resulting from insufficiencies or inadequacies in the instruction for use, deployment, or any malfunction of the medical device, as well as any event resulting from use error or from intentional misuse of the device.

Table 2 lists anticipated adverse device effects that may occur.

Table 19-1 Anticipated adverse device effects and their likely incidence rates

ANTICIPATED ADE	INCIDENCE RATE
Urinary tract infection	Very unlikely
Macroscopic haematuria	Unlikely
Macroscopic leukocytes	Unlikely
Stinging and pain in urethra during catheterisation	Likely
Irritation of mucosa	Likely

19.3 Device deficiency

A device deficiency is the inadequacy of the investigational medical device or comparator with respect to its identity, quality, durability, reliability, usability, safety, or performance. This includes malfunctions, use errors and inadequacy in the information supplied by the manufacturer including labelling.

19.4 Serious adverse events (SAE)

A serious adverse event is an adverse event that:

- Led to death,
- Led to a serious deterioration in the health of the subject, users or other persons as defined by one or more of the following:
  1) a life-threatening illness or injury, or
  2) a permanent impairment of a body structure or a body function including chronic diseases, or
  3) in-patient or prolonged hospitalization, or
  4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.

- Led to foetal distress, foetal death, a congenital abnormality, or birth defect including physical or mental impairment.

This includes device deficiencies that might have led to a serious adverse event if:

1) Suitable action had not been taken, or
2) Intervention had not been made, or

3) Circumstances had been less fortunate.

These are handled under the serious adverse event reporting.

Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

19.4.1 Serious adverse device effect (SADE)

A serious adverse device effect is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

19.4.2 Anticipated serious adverse device effect (ASADE)

There are no anticipated SADEs.

19.4.3 Unanticipated serious adverse device effect (USADE)

An unanticipated serious adverse device effect is a serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report.

19.5 Medical care of subjects

Principal investigator shall ensure that adequate medical care is provided, during and after participation in the clinical investigation, to a subject experiencing an adverse event. All ongoing ADEs, SAEs, SADEs and DDs that could have led to a SAE at subject termination will be followed according to the Risk Benefit analysis (see section 9). An ongoing adverse event at subject termination visit is documented as the current status for the adverse event and will not be followed up.

The subjects shall be informed of any new significant findings occurring during the clinical investigation, including the need for additional medical care that can be required, and of the nature and possible cause of any adverse events experienced.

19.6 Reporting and timelines

All adverse events and device deficiencies will be reported in the eDC, Rave database. If, for some reason, the system is off-line, investigators (or designee) are required to report the event to: **clinical-studies@coloplast.com.**

19.7 Investigator's reporting responsibilities

PI at each site must assess all (S)AE`s that occur at his/her site.

- All serious adverse events and serious adverse device effects must be reported to sponsor within 24 hours of the site becoming aware of the event.
- A device deficiency that could have led to a serious adverse event but did not because suitable action was taken, intervention had been made or because of fortunate circumstances should be reported to sponsor within 24 hours of the site becoming aware of the event.
- New findings and/or updates in relation to already reported serious events should also be reported to sponsor within 24 hours of the site becoming aware of the event.
- Device deficiencies and all adverse device effects related to CE marked Coloplast investigational device and/or comparator must be reported to sponsor within 24 hours of becoming aware of the event.

When reporting the SAE, the relationship to the test material shall be described whether the event is considered

- **Not related**, the event has no temporal relationship with the use of the test material or the procedures.
- **Unlikely related,** the relationship with the use of the test material seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
- **Possible related,** the relationship with the use of the test material is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.
- **Probable related,** the relationship with the use of the test material seems relevant and/or the event cannot reasonably be explained by another cause, but additional information may be obtained.
- **Definitely related/Causal relationship,** the event has a temporal relationship with the test material use/application or procedures.

and the intensity of the event should be considered, as such:

- **Mild,** the intensity of the event is mild with no further action or intervention
- **Moderate,** the intensity of the event will lead to an action or intervention to solve the event
- **Severe,** the intensity of the event will lead to follow up on the action or intervention, as the effect of the action or intervention may not decrease the symptoms.

All above events must be reported by use of the relevant adverse event/serious adverse event/device deficiency form and sent to: clinical-studies@coloplast.com

In cases where accessing e-mail is not possible, please report to:

For Denmark	For United Kingdom	For Germany	For France
[redacted] dksths@coloplast.com	[redacted] dksths@coloplast.com	[redacted] dksths@coloplast.com	[redacted] dksths@coloplast.com

19.8 Sponsors reporting responsibilities

It is the responsibility of sponsor to ensure that the following are reported to national regulatory authorities immediately, but no later than 7 calendar days following the date of awareness by sponsor.

- All serious adverse events.
- All serious device effects.
- All device deficiencies that could have led to serious adverse events but did not because suitable action was taken, intervention had been made or because of fortunate circumstances.
- New findings and/or updates in relation to already reported events.

If the serious adverse event results in imminent risk of death, serious injury, or serious illness that requires prompt remedial action for other subjects, users or other persons or a new finding to such a serious adverse event, sponsor must immediately but no later than 2 calendar days after awareness by sponsor report the event to national regulatory authorities.

It is the responsibility of sponsor to inform all investigators in writing within 10 working days if device deficiencies, adverse events, adverse device effects, near-incidents, serious adverse events, serious adverse device effects or unanticipated serious adverse device effects lead to corrective actions (*e.g.* change of IFU).

20 Suspension or premature termination of the clinical investigation

Sponsor may suspend or prematurely terminate an investigation site or the entire clinical investigation for documented significant reasons.

If a suspicion of an unacceptable risk to subjects develops during the clinical investigation, sponsor will suspend the investigation while the risk is assessed. Sponsor will terminate the investigation if an unacceptable risk is confirmed. Sponsor will ensure that the premature termination will be justified in writing and will promptly inform the regulatory authorities and relevant EC(s). If monitoring or auditing of the clinical investigation identifies serious or repeated deviations at one of the participating investigation sites, sponsor will suspend or terminate the particular investigational site. The sponsor or investigator will inform the regulatory authority as appropriate and notify the EC about the termination of the site.

21 Clinical investigation report

At completion of the investigation, sponsor is responsible for writing the clinical investigation report. The report is retained on file. The report contains a critical evaluation of all data, which have been collected during the investigation. The report describes the methodology and design and a data analysis, including statistical preparation and conclusion.

Sponsor and national coordinating investigators must sign the final version of the clinical investigation report or an affidavit, indicating their agreement with the contents. If no coordinating investigators are appointed, then the signatures of the principal investigators should be obtained.

The clinical investigation report will be submitted to Ethics Committee and local regulatory authorities.

22 Publication policy

Coloplast, sponsor, is referring to the internal document 'Clinical Publication Policy' that will be available for internal and external persons involved in the publication process.

The investigation will be registered in a publicly accessible database before recruitment of the first subject. The results of the investigation, positive as well as inconclusive and negative will be published in the same publicly accessible database. The subjects' identity will remain confidential. Publication of results in the database will be conducted per the law of personal data protection and will be initiated as soon as scientifically acceptable, however, within one year after the last subject has completed the investigation. Data from the investigation is considered confidential until it is published per the conditions of this Clinical Investigation Plan and the 'Clinical Publication Policy'. Sponsor may publish anonymous single subject case stories (or public, if the subject consents) at any time during and after the investigation. The identification of the participant must not be possible. Sponsor reserves the right to use the data (published and unpublished) for reimbursement or regulatory purposes.

23 Suspension/termination of the clinical investigation

Sponsor will withdraw from sponsorship of the clinical investigation if

- major non-adherence to the clinical investigation plan is occurring
- it is anticipated that the subject recruitment will not be adequate to meet the investigation objectives at least 75% of the subjects should be entered within the recruitment time.

In case sponsor withdraws, sponsorship for the subjects already recruited into the clinical investigation will continue.

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25 Appendix A - Perception Questionnaire

25.1 Perception questionnaire – Part I

Handling	Very difficult	Difficult	Neither Difficult nor Easy	Easy	Very easy	Don't know
How was it to insert the catheter?	☐	☐	☐	☐	☐	☐
How was it to empty the bladder?	☐	☐	☐	☐	☐	☐
How was it to withdraw/remove the catheter?	☐	☐	☐	☐	☐	☐
How was it to perform a hygienic catheterization?	☐	☐	☐	☐	☐	☐
How was it to use the catheter?	☐	☐	☐	☐	☐	☐
Confidence and in control	Strongly disagree	Disagree	Neither disagree nor agree	Agree	Strongly agree	Don't know
I feel in control when inserting the catheter	☐	☐	☐	☐	☐	☐
I feel confident when inserting the catheter	☐	☐	☐	☐	☐	☐
I feel in control when withdrawing the catheter	☐	☐	☐	☐	☐	☐
I feel confident when withdrawing the catheter	☐	☐	☐	☐	☐	☐
I do not experience urine running on the outside surface of the catheter (also called "bypass urine")	☐	☐	☐	☐	☐	☐
I need to withdraw the catheter in small steps to completely empty my bladder	☐	☐	☐	☐	☐	☐
I need to turn/rotate the catheter to completely empty my bladder	☐	☐	☐	☐	☐	☐
I need to withdraw the catheter very slowly to completely empty my bladder	☐	☐	☐	☐	☐	☐
I feel confident my bladder is completely emptied when the urine flow stops	☐	☐	☐	☐	☐	☐
I feel confident the catheter empties my bladder completely	☐	☐	☐	☐	☐	☐
Sensation	Strongly disagree	Disagree	Neither disagree nor agree	Agree	Strongly agree	Not applicable (lack of sensation)
It feels gentle to insert the catheter	☐	☐	☐	☐	☐	☐
It feels gentle to withdraw the catheter	☐	☐	☐	☐	☐	☐
I have felt resistance during withdrawal	☐	☐	☐	☐	☐	☐
I have felt a blocking sensation during catheterization	☐	☐	☐	☐	☐	☐
I have felt pinching/stinging during catheterization	☐	☐	☐	☐	☐	☐
Satisfaction	Strongly disagree	Disagree	Neither disagree nor agree	Agree	Strongly agree	Don't know
I am satisfied with the catheter	☐	☐	☐	☐	☐	☐
I would recommend the catheter to others	☐	☐	☐	☐	☐	☐

25.2 Perception questionnaire – Part II

When the urine flow stops, do you reposition the catheter? (reposition = withdraw the catheter in small steps and/or turning/rotating the catheter)

- ☐ Yes
- ☐ No
- ☐ Don't know

After removing the catheter, are you certain that the bladder is completely empty?

- ☐ Yes
- ☐ No
- ☐ Don't know

26 Appendix B – Qualiveen-30

26.1 QUALIVEEN-30

How to answer the questionnaire:
The following questions are about the bladder problems you may have and how you deal and live with them. When answering the questions, think about how you passed urine over the past two weeks.

Please fill in this questionnaire in a quiet place and preferably on your own. Take the time you need. There are no right or wrong answers. If you are not sure how to answer a question, choose the answer which best applies to you. Please note that your answers will remain strictly anonymous and confidential.

When answering the questions, think about how you pass urine over the past two weeks.
Thank you for your participation.
Please answer all the questions by ticking the appropriate box.

	Are you bothered by*: **If you have no concern about one or several questions above, answer "Not at all"*	Not at all	Slightly	Moderately	Quite a bit	Extremely
1.	urine leaks during the day	☐	☐	☐	☐	☐
2.	urine leaks at night	☐	☐	☐	☐	☐
3.	having to wear continence - pads/penile sheaths - indwelling catheter/ suprapubic catheter	☐	☐	☐	☐	☐
4.	being dependent on a timetable for passing urine or realizing catheterisation during your activities	☐	☐	☐	☐	☐
5.	the time spent passing urine or realizing catheterisation	☐	☐	☐	☐	☐
6.	because your nights are disturbed	☐	☐	☐	☐	☐
7.	when away from home or travelling	☐	☐	☐	☐	☐
8.	personal hygiene problems when away from home	☐	☐	☐	☐	☐
9.	**In general,** do your bladder problems complicate your life?	☐	☐	☐	☐	☐
		Never	Rarely	From time to time	Often	Always
10.	Can you go out without planning anything in advance	☐	☐	☐	☐	☐
11.	Have you given up going out	☐	☐	☐	☐	☐
12.	Are you more dependent on others, due to your bladder problems	☐	☐	☐	☐	☐
13.	Is your life regulated by your bladder problems	☐	☐	☐	☐	☐
	Are you forced to:	Never	Rarely	From time to time	Often	Always
14.	plan everything	☐	☐	☐	☐	☐
15.	think about taking a change of clothes and/or continence pads/penile sheaths protections with you	☐	☐	☐	☐	☐
16.	wear continence pads/penile sheaths as a precaution	☐	☐	☐	☐	☐
17.	be careful about how much fluid you drink	☐	☐	☐	☐	☐

26.2 QUALIVEEN-30 - *continued*

	Do you worry about:	Not at all	Slightly	Moderately	Quite a bit	Extremely	Not applicable
18.	smelling of urine	☐	☐	☐	☐	☐	
19.	having urinary infections	☐	☐	☐	☐	☐	
20.	your bladder problem worsening	☐	☐	☐	☐	☐	
21.	disturbing your partner at night	☐	☐	☐	☐	☐	☐
22	having urine leaks during sexual intercourse	☐	☐	☐	☐	☐	☐
23.	having side effects from the drugs you take	☐	☐	☐	☐	☐	
24.	having skin problems	☐	☐	☐	☐	☐	
25.	having money problems due to the expenses involved with your bladder problems	☐	☐	☐	☐	☐	

	Do you feel:	Not at all	Slightly	Moderately	Quite a bit	Extremely
26.	embarrassed because of your bladder problems	☐	☐	☐	☐	☐
27.	a loss of self-respect because of your bladder problems	☐	☐	☐	☐	☐
28.	a need to conceal your bladder problems	☐	☐	☐	☐	☐
29.	worried about other people's reactions if you have to spend a long time in the toilet	☐	☐	☐	☐	☐
30.	worried because of your bladder problems	☐	☐	☐	☐	☐