Clinical Investigation Plan

CP356

A randomized, crossover study confirming performance of a new single-use compact intermittent catheter vs. Infyna Chic in a population of adult female intermittent catheter users.

April 2023 – October 2023

Master

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CHANGE LOG

VERSION NUMBER	ISSUED BY *(INITIALS)*	COMMENTS (MAJOR CHANGES SINCE LAST REVISION)
1.0	[redacted]	*First approved version*
2.0		*Changes to no remuneration for Visit 0 "information visit"*

SYNOPSIS OF THE CLINICAL INVESTIGATION

Title:

A randomized, crossover study confirming performance of a new single-use compact intermittent catheter vs. Infyna Chic in a population of adult female intermittent catheter users.

Test products 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 new compact single-use intermittent catheter will be available in sizes CH12 and CH14 for females in this clinical study.
The investigational devices are not CE-marked in EU, and they will be provided by Coloplast A/S, Denmark.
The comparator is Hollister Infyna Chic, a CE-marked single-use compact catheter.

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.

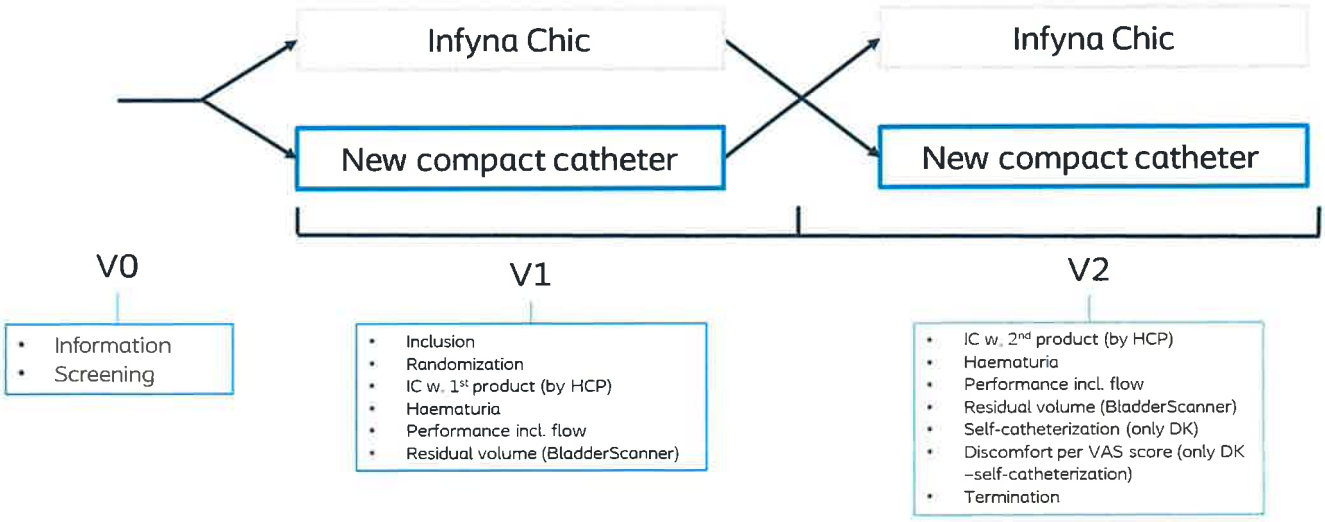
Objective(s)

Primary Objective: To demonstrate superiority of the new compact catheter in terms of improved bladder emptying, with the catheterization performed by a health care professional (HCP).

Secondary objective: Is to assess safety of the new compact catheter in support of the CE marking.

Design of the investigation

The study is a randomised, single-blinded, controlled crossover study.
The total study duration for the individual subject will be between two days - two weeks, consisting of three site visits. Visits 0 and 1 can be performed on the same day. Visit 2 can be performed the day after visit 1.
For visit 1 and 2, catheterizations will be performed in a hospital setting by a health care professional for bladder emptying assessment and collection of urine samples for haematuria assessment. A sub-group of subjects (all enrolled subjects at DK sites) will be asked to conduct a self-catheterization at visit 2 after hcp catheterization and evaluate discomfort and PVR.



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): June 2023

Last patient in (LPI): October 2023

Last patient out (LPO) October 2023

Database lock (DBL): November 2023

Primary endpoint and secondary endpoint(s)

Primary endpoints:

- Residual volume at 1st flow-stop i.e., post catheterisation volume minus volume at 1st flow-stop, both derived from a catheterisation profile, [mL].

Secondary endpoints:

- Number of flow-stop episodes derived from a catheterisation profile (catheterisation performed by a healthcare professional), [number].
- Average residual volume post catheterisation (PVR) measured with a bladder scanner (triplicate measurements), [mL],
- Number of Adverse events, [number]

Population/subjects

The clinical study will be conducted in Denmark and the UK where a total of 72 subjects will be included in the clinical study.

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

Inclusion criteria	Exclusion criteria
1. Is Female	1. Is participating in any other clinical study during this investigation
2. Is at least 18 years of age and has full legal capacity	2. Has previously participated in this study
3. Has signed an informed consent form	3. Has symptoms of urinary tract infection at time of inclusion, as judged by the investigator (if the patient recovers within the recruitment period, a second inclusion is allowed, under a different subject id)
4. Has used clean intermittent catheterisation (CISC) CH12 or CH14 for at least one month up to inclusion	4. Is an individual with history of – suspected to be - or showing signs of producing excessive amount of mucus, large/clustered sediments or debris
5. Is using intermittent self-catheterisation for a minimum of 3 times daily for bladder emptying.	5. Has any known allergies towards ingredients in the investigational device
6. Has used a compact catheter 50% of the time (or more) for the last 2 weeks prior to inclusion in the study or is able to use a compact catheter assessed by investigator	6. Is pregnant
7. Has the ability (assessed by investigator) and willingness to follow study procedures	7. Is breastfeeding

LIST OF ABBREBIATIONS

ABBREVIATION	WRITTEN OUT	EXPLANATION
ADE	Adverse Device Effect	See section 18.2
AE	Adverse Event	See section 18.1
ASADE	Anticipated Serious Adverse Device Effect	See section 18.4.2
CIP	Clinical Investigation Plan	
CRF	Case Report Form (paper or electronic)	Questionnaire to be used for data collection
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	
EC	Ethics Committee	
HCP	Health Care 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.
IFU	Instruction For Use	
ITT	Intention to Treat	
PI	Principal Investigator	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.
PP	Per Protocol	
SADE	Serious Adverse Device Effect	See section 18.4.1
SAE	Serious Adverse Event	See section 18.4
USADE	Unanticipated Serious Adverse Device Effect	See section 18.4.3
UTI	Urinary Tract Infection	

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1. List of personnel involved in the Investigation

COORDINATING CLINICAL MANAGER	HEAD OF CLINICAL TRIAL MANAGEMENT
[redacted]	[redacted]
ASSOCIATE CLINICAL MANAGER	**DATA MANAGEMENT SPECIALIST**
[redacted]	[redacted]
PRINCIPAL BIOSTATISTICIAN	**MEDICAL AFFAIRS PROJECT MANAGER**

In case of emergency, please contact the Clinical Manager/Clinical Monitor from the above list of sponsor representatives.

2. Rational/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 has developed a new intermittent compact catheter for females, 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 safety and performance of this new compact catheter compared to a conventional 2-eyelet catheter.

3. Objective(s) and hypotheses of the clinical investigation

3.1. Objective (s)

Primary objective: To demonstrate superiority of the new compact catheter in terms of improved bladder emptying, with the catheterization performed by a health care professional.

Secondary objective: Is to assess safety of the new compact catheter in support of the CE marking

3.2. Hypotheses

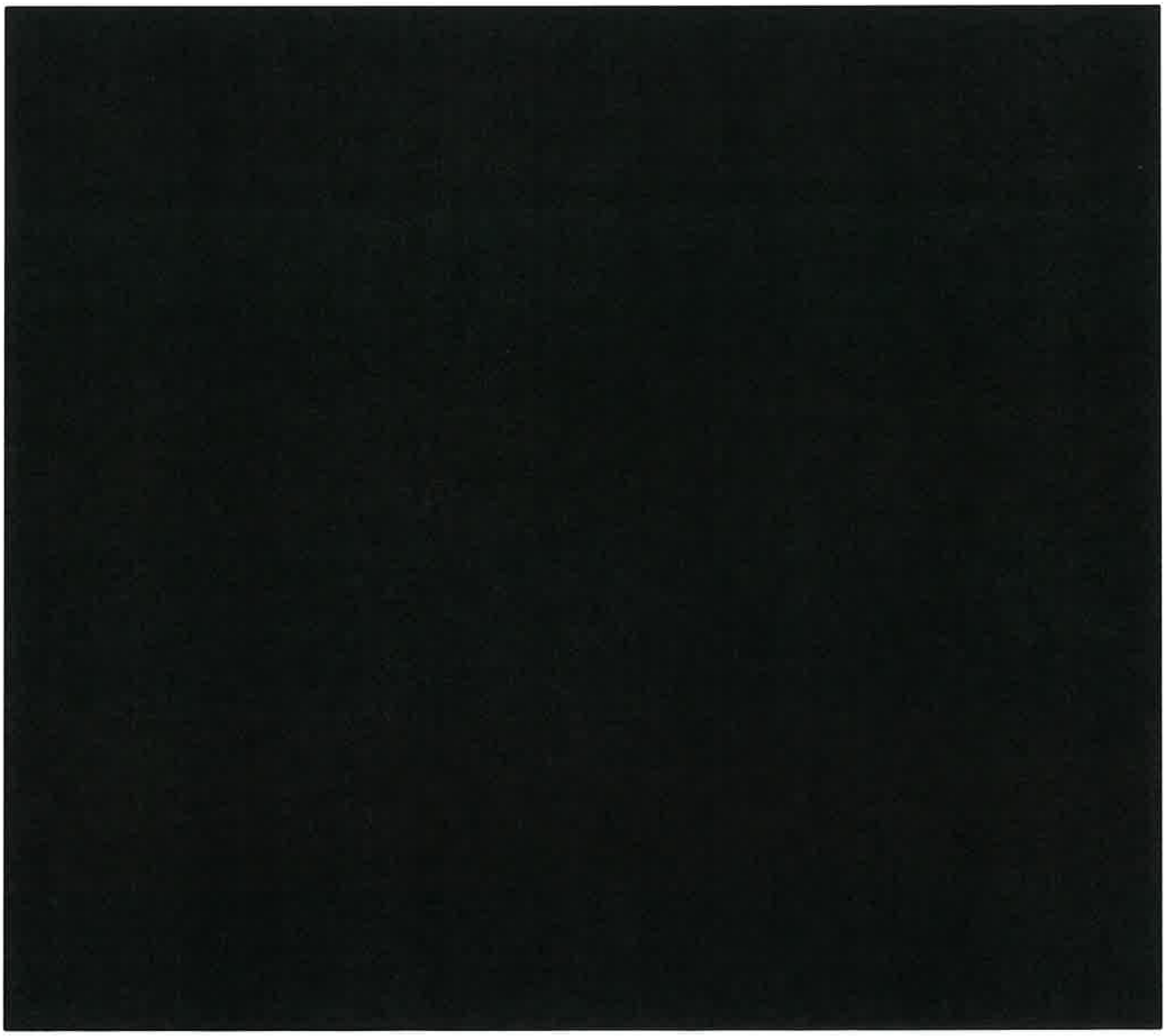
The aim is to assert the hypothesis of the superiority of a newly developed compact catheter over Infyna Chic, a conventional 2-eyelet catheter with lower residual volume at 1st flow-stop.

4. Investigational device and comparator

4.1. Description of investigational device

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

The device is intended to be used by female catheters users in this clinical study.



4.1.1. Manufacturing

Responsible for manufacturing the investigational device:
Coloplast A/S
Holtedam 1
3050 Humlebæk
Denmark.

4.2. Identification and traceability of the device

All investigational devices are labelled as per regulations and included "exclusively for clinical investigation" on the label. The devices are also identified with a study number, device name/code, and item/lot number and is accounted for through a sponsor accountability log.

Upon EC/CA approval, 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.

4.3. Intended use of the device in the clinical investigation

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

4.4. Intended population for the device

The eligible population is female 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.

4.5. 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. All training will be documented.

For further details regarding the test device, please refer to the Investigators Brochure VV-0518891

4.6. Total number of devices intended for the clinical investigation

Seventy-two subjects will be included in the study and have a catheterization performed in a randomized order with the investigational device or comparator, so the total use is 144 catheters.

4.7. Description of the comparator product

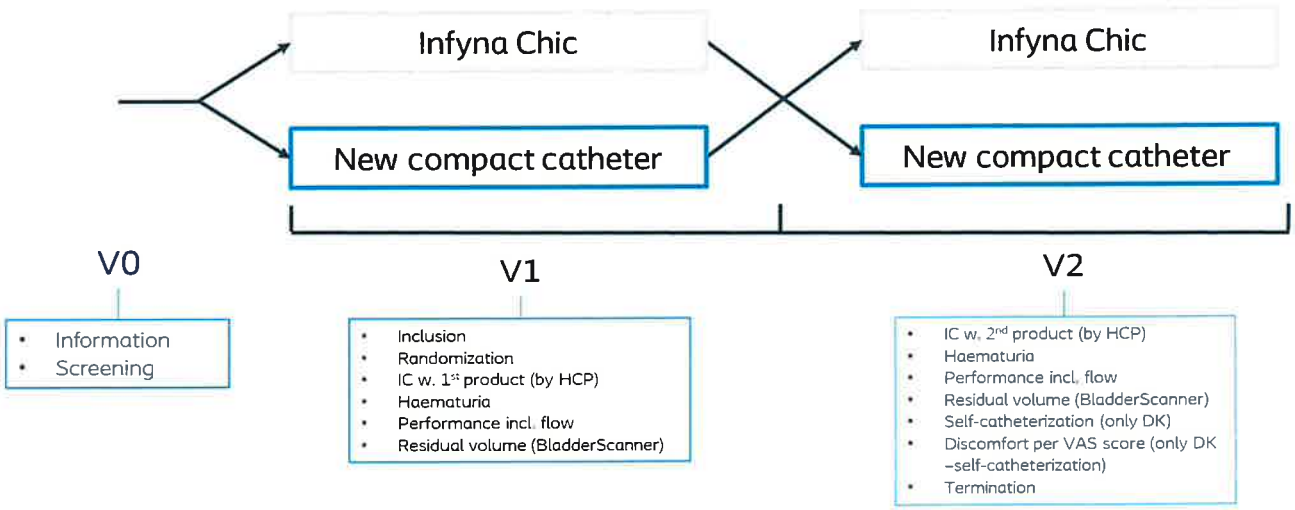
The comparator is Hollister Infyna Chic, a single-use hydrophilic soft/flexible catheters in the sizes CH12 or CH14. Hollister Infyna Chic is CE-marked in EU

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 A/S will provide comparator devices to sites. To ensure that the site has enough supplies, more investigational devices than needed will be provided by Coloplast.

5. Design of the clinical investigation

5.1. General

The study is a randomised, single-blinded controlled crossover study. The total study duration for the individual subject will be between 2 days – 14 days consisting of three site visits. Visits 0 and 1 can be performed on the same day, and it is possible to perform visit 1 and visit 2 on two consecutive days. For visit 1 and 2, catheterizations will be performed in a hospital setting by a health care professional for bladder emptying assessment and collection of urine samples for haematuria assessment.
A sub-group of subjects (all enrolled subjects at DK sites) will be asked to conduct a self-catheterization at visit 2 after HCP catheterization and evaluate discomfort and PVR.



(Figure 5-1) Randomized controlled crossover investigation with two products.

5.2. Primary endpoint

- Residual volume at 1st flow-stop i.e., post catheterisation volume minus volume at 1st flow-stop, both derived from a catheterisation profile, *[mL]. (Catheterisation by HCP)*

5.3. Secondary endpoints

- Number of flow-stop episodes derived from a catheterisation profile (catheterisation performed by a healthcare professional), [number].
- Average residual volume post catheterisation (PVR) measured with a bladder scanner (triplicate measurements), [mL],
- Number of Adverse events, [number]

5.4. Assessments

Assessments (Catheterisation performed by the HCP):

- Position of the subject when performing the catheterisation, [sitting/standing]
- Catheter used for catheterisation (Test Product/Comparator, including catheter size (CH12/CH14))
- Urine volume from 2nd until 10th flow stop (derived from catheterisation profile), [mL]
- Urine volume measured post catheterisation (derived from catheterisation profile), [mL]
- Is subject menstruating at visit (yes/no)

Backup assessments (recorded by the HCP to replace endpoints if needed, in case of damaged profile recordings and/or readouts):

- Urine volume at 1st flow stop (scale), [g].
- Urine volume measured post catheterisation (scale), [g]
- Urine volume pre-catheterisation measured with a bladder scanner (triplicate measurements), [mL]
- Time for start of catheterization ([HH+:nn],[hours and minutes]
- Number of flow-stop episodes counted by HCP, [number]

Haematuria assessed by dipstick:

- Dipstick specific gravity, post catheterisation
  - (1.000/1.005/1.010/1.015/1.020/1.025/1.030)
- Dipstick haematuria, post catheterisation, [7-point scale]
  - Non-haemolysed – 0 Ery/ul (NEGATIVE)
  - Non-haemolysed – 10 Ery/ul (+/) (NEGATIVE)
  - Non-haemolysed – 80 Ery/ul (2+) (POSITIVE)
  - Haemolysed – 10 Ery/ul (+/-) (NEGATIVE)
  - Haemolysed – 25 Ery/ul (1+) (POSITIVE)
  - Haemolysed – 80 Ery/ul (2+) (POSITIVE)
  - Haemolysed – 200 Ery/ul (3+) (POSITIVE)
- Dipstick leukocyturia post catheterisation, [5-point scale]
  - 0 Leu/µL - Negative
  - 15 Leu/µL - (1+)
  - 70 Leu/µL - (2+)
  - 125 Leu/µL - (3+)
  - 500 Leu/µL - (4+)

Assessments on subgroup all enrolled subjects at DK sites (Self-catheterisation):

- Urine volume pre-catheterisation measured with a bladder scanner (triplicate measurements), [mL]
- Position of the subjects when performing the catheterisation, [sitting/standing]
- Catheter used for catheterisation (Test product/comparator, including size (CH12/CH14))

- Residual volume post catheterisation (PVR) measured with a bladder scanner (triplicate measurements) [mL]
- Discomfort at insertion measured using the visual analog scale (VAS) [cm]
- Discomfort at withdrawal measured using the VAS [cm]
- Discomfort during emptying of bladder measured using the VAS [cm]
- Discomfort at end of emptying the bladder measured using the VAS [cm]

5.5. 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. Both inadequate bladder emptying and urethral/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).
The event has been reproduced with intermittent catheters in a porcine bladder model in a pre-clinical setting at Coloplast (Tentor, 2022) and 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 catheterisation.
RV1 is measured *in* catheterisation by HCP and by self-catheterisation *as it* allows for comparison between catheters during an expectedly correctly applied catheterisation technique.

Microtrauma: Concentration of microscopic haematuria and incidences of positive haematuria indicates possible catheter-associated microtrauma. With the catheter with micro-holes, 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).

5.6. Equipment/methods and timing for assessing the variables

Supplementing devices or instruments normally used for catheterization. Scales for measurement of total amount of urine, ultrasound scanner measuring residual urine [BladderScan i10, Verathon Inc.], container, funnel for urine collection, dipsticks used for measuring hematuria and pregnancy test will be provided by Coloplast A/S.

5.7. 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:

- First sequence: Investigational device (Visit 1), then the comparator (Visit 2)
- Second sequence: The comparator (Visit 1), then the investigational device (Visit2).

Participants will be randomly assigned to the two intervention sequences in block sizes of 8.

Randomisation will be centralized using the web-based iMedidata RAVE RTSM™, see section 11.

5.8. Blinding

Subjects will not be blinded in this investigation due to inclusion of self-catheterisation. Furthermore, personnel present at the catheterisation i.e. nurses, and assisting Coloplast personnel are also not blinded. Coloplast personnel not present at the catheterisation i.e. the statistician, the specialists analysing the catheterisation profiles, and project manager will be blinded until the data base lock. Clinical Managers, CRAs and the Data Management Specialist are not blinded due to insight to the investigation database.

5.9. 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): June 2023

Last patient in (LPI): October 2023

Last patient out (LPO): October 2023

Database lock (DBL): November 2023

6. Clinical Investigation population

The clinical study will be conducted in Denmark and the UK where a total of 72 subjects will be enrolled in 8 investigational sites.

6.1. Eligibility criteria

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

6.1.1. Inclusion criteria

Inclusion criteria	Justification for inclusion criteria
1. Is female	Intended patient population of investigational and comparator devices.
2. Is ≥18 years of age	Intended patient population of investigational and comparator devices. To meet Helsinki Declaration.
3. Has signed an informed consent form	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 used clean intermittent catheterisation (CH12 or CH14) for at least one month up to inclusion.	To ensure that the subject is used to catheterization.
5. Is using intermittent self-catheterisation for a minimum of 3 times daily for bladder emptying	To ensure that the subject is used to catheterization.
6. Has used a compact catheter 50% of the time (or more) for the last 2 weeks prior to inclusion in the study or is able to use a compact catheter assessed by investigator	To ensure that the subject can use the investigational device.
7. Has the ability (assessed by investigator) and willingness to follow study procedures	To ensure sufficient data for successful completion of the study.

6.1.2. Exclusion criteria

Exclusion criteria	Justification for inclusion criteria
1. Participate in any other clinical study during this investigation	Intended patient population of investigational and comparator devices.
2. Has previous participated in this study	Intended patient population of investigational and comparator devices. To meet Helsinki Declaration.
3. Has symptoms of urinary tract infection at time of inclusion, as judged by the investigator (if patient recover within the recruitment period, a second inclusion is allowed, under a different subject id.)	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. Is an individual with history of – suspected to be - or showing signs of producing excessive amount of mucus, large/clustered sediments or debris	To ensure subject's safety and integrity of results
5. Has any known allergies towards ingredients in the investigational device	To ensure subject's safety and integrity of results
6. Is pregnant	Even though the ingredients and the recipes have been approved for human beings, their effect on embryos, fetuses and infants are unknown
7. Is breastfeeding	Even though the ingredients and the recipes have been approved for human beings, their effect on embryos, fetuses and infants are unknown

6.1.3. Pregnancy and breastfeeding

For female subjects with childbearing potential (they have had at least one period during the last 12 months), a urine pregnancy test will be performed at the inclusion visit, to ensure the subject is not pregnant. The urine pregnancy test will be performed by dip-stick at the trial site. Furthermore, the female subjects should not be breastfeeding, when participating in the clinical investigation.

If the subject is sexually active, she should be willing to practice appropriate contraceptive methods until the end of the investigation. Appropriate contraceptive methods are: sexual abstinence (in some cases when the women are older than 50 years, but are not yet post-menopausal, the investigator may evaluate that it is not reasonable to ask these women to start using safe contraceptives for the duration of the investigation); oral contraceptives, trans dermal patches or depot injection of a progestogen drug, double barrier method: condom or occlusive cap (diaphragm or cervical/vault caps) plus spermicidal agent; intrauterine device (IUD), intrauterine system (IUS), implant, or vaginal ring (placed at least 4 weeks before the first test period); or male partner sterilization before the female participant's entry into the investigation and is the sole sexual partner for that female participant. However, national requirements should always be followed. If the subject becomes

pregnant during the investigation, it is important, that the subject informs the Investigator/Investigator representative immediately.

6.2. Recruitment and enrolment

6.2.1. Recruitment process

The recruitment of potential subjects will only commence once authorisation and approval has been received from the Regulatory Authorities (if applicable) and Ethics Committee (EC). The recruitment period from first subject enrolled to last subject enrolled is expected to be approximately 16 weeks.

Overview of the recruitment process

Recruitment method	Outpatient clinic/hospital	Advertising	Coloplast Database
Potential subjects	Recruitment will go through the outpatient clinic/ hospital site. Potential subjects are qualified by the inclusion criteria described in section 6.1.1	Recruitment will go through advertising in relevant channels of online and offline media (e.g., posters, social media, online paid media etc.). For the online channels, potential subjects will be directed to a landing page with a self-screener that qualifies the subjects in accordance with the inclusion criteria described in section 6.1.1 For the offline channels, study duration and screening criteria will be listed, and subjects are encouraged to contact the PI for further information.	Recruitment will go through the Coloplast database, where potential subjects are contacted by email. Subjects are selected according to the inclusion criteria described in section 6.1.1 and include: age, gender, product usage, type, size, and permission status. If the subjects are interested, they will be directed to a landing page, where eligibility is confirmed through a self-screener that qualifies subjects in accordance with the inclusion criteria.
First contact	Potential subjects will be contacted by email, phone call or contacted during a planned visit in the outpatient clinic at the hospital. If a subject is eligible and interested in participating in the investigation upon a short introduction, then written information about the investigation (Subject Information Form/Informed Consent Form) will be distributed to the subject. The Principal Investigator or delegate will invite the subject to a Screening Visit (V0).	Potential subjects will via the advertisement be directed to a landing page with a self-screener. If a subject qualifies for the study, telehealth nurses will call the subject to verify eligibility. A list of all eligible subjects is sent to site, where a final screening call is conducted to reconfirm eligibility. If subjects qualify and are interested in participating, a date for V0 is agreed and written information about the investigation (Subject Information	Potential subjects from the database will be contacted by email. Potential subjects will via the emails be directed to a landing page with a self-screener, and if a subject qualifies for the study, telehealth nurses will call the subject to verify eligibility. A list of all eligible subjects is sent to site, where a final screening call is conducted to reconfirm eligibility. If subjects qualify and are interested in participating, a date

Recruit-ment method	Outpatient clinic/hospital	Advertising	Coloplast Database
		Form/Informed Consent Form) is sent to the subject.	for V0 is agreed and written information about the investigation (Subject Information Form/Informed Consent Form) is sent to the subject.
Screening visit (V0)	At the scheduled Screening Visit (V0) the Principal Investigator or delegate will introduce the investigation and review the inclusion and exclusion criteria. If the subject wishes to reconsider her participation at V0, the subject has the right to wait a minimum of 24 hours before deciding on participation. If the subject hereafter decides to participate in the clinical investigation a Baseline Visit (V1) will be scheduled unless performed the same day as the Screening Visit. The Screening Visit can be performed at the site or as a phone call. If the subject does not meet the inclusion criteria or meets the exclusion criteria, this will be registered at the Subject Pre-Screening Log.		
Baseline visit (V1)	If the subject decides to participate and it is certain that it is understood what the investigation entails, the subject will be asked to sign the SIF/ICF. When the SIF/ICF is signed, the subject is considered included in the investigation.		

6.3. 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. At least three documented attempts will be made to verify subjects lost to follow-up.

Randomized subjects that for some reason withdraw from the clinical investigation can be replaced. Replacements should be discussed with Sponsor. Please also refer to section 10.2 Sample size for further information.

6.4. Screening Failures and drop-outs

Subjects that have signed the informed consent form but fail to comply with inclusion or exclusion criteria are considered screening failures (until randomization).

After randomization you are considered as a drop-out

6.5. Point of enrolment

A subject is considered enrolled in the investigation at the time at which, following recruitment and before any clinical investigation-related procedures are undertaken, the subject signs and dates the informed consent form.

6.6. Subject Identification and Confidentiality

Subjects will be identified in the electronic CRF (eCRF) 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 eCRF are confidential and will only be available to the sponsor (including sponsor delegates), members of data management teams, the statistician, members of the EC 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 included into the clinical investigation.

7. Procedures

7.1. Catheterisation set-up

Subjects are not allowed to lay down during catheterisation. Only sitting at minimum 45 degrees angle or standing is optional (V1 and V2). The position used for the HCP catheterisations must be the same at both visits.
At V1 and V2 it is important to ensure free urine flow from catheter outlet into urine collection container placed on scale. Urine collection container must remain untouched during catheterisation.

NB! HCP should count to 3 sec. if suspicious of a flow-stop before rotating the catheter to make it more clear on the profile.

7.2. Clinical investigation-related procedures

Screening Visit 0 (V0)

- Introduction to the investigation and review of Informed Consent Form/Subject Information Form
- Check of in- and exclusion criteria
- Scheduling Baseline Visit (V1) unless performed the same day as Screening visit (V0)
- Register the potential subject on the Pre-screening Log if not already registered

Baseline Visit 1 (V1):

- Introduction to the investigation reviewed and confirmed
- Sign informed consent form
- Enrolment in the investigation and allocation of subject number
- Check of in- and exclusion criteria
- For female subjects of childbearing potential: urine pregnancy dipstick
- Relevant medical history (assessed by the investigator)
- Collect Baseline information
  - Age (at time of enrolment in years)
  - Height (in cm)
  - Weight (in kg)
  - Reason for using intermittent catheterisation
    - Spinal cord injury
    - Multiple sclerosis
    - Spina bifida

    - Others (as text)
- Neurogenic/Non-neurogenic
- Body mobility / ambulation
    - Walking
    - Walking with difficulty/aids
    - Using a wheelchair
    - Confined to bed
- When did you start using a catheter? (year + month (if known))
- Current primary product
    - Coloplast: SpeediCath Compact Female, SpeediCath Compact Female Plus, SpeediCath Compact Eve,
    - Wellspect: Lofric Sense, Lofric Elle
    - Hollister: Infyna Chic, Vapro Pocket
    - B. Braun: Actreen Mini
    - Bard: Hydrosil Rose, Hydrosil GO, Magic3Go
    - Convatec: GentleCath Air Female
    - Curan: Curan Lady (Curan Twist in US)
    - Other (text)
- Current product size (CH12, CH14)
- Position most frequently used when catheterizing with current product
    - Sitting
    - laying
    - standing
    - other (text)
- Urethral sensation
    - Normal
    - Impaired
    - None
    - Hypersensitive
- Average number of catheters used per day [number]
- 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/right)?
- Left hand:
        - Normal dexterity
        - Reduced dexterity
        - Greatly reduced dexterity
        - Don´t know
- Right hand:
        - Normal dexterity
        - Reduced dexterity
        - Greatly reduced dexterity
        - Don´t know

- Review of concomitant medication potentially affecting urinary function (assessed by investigator) and pain management at time of enrolment
- Information regarding menstrual cycle
- Randomization
- Pre-catheterization volume measured in triplicate with a bladder scanner. All measurements must be above 150 ml to proceed

- Catheterisation with 1st randomly assigned product (by HCP)
  - **NB!** HCP should count to 3 sec. if suspicious of a flow-stop before rotating the catheter to make it more clear on the profile.

- Catheterization profile (urine volume + number of flow stops)
- Volume at 1st flow stop and post catheterization volume noted from scale
- Number of flow stops noted
- Catheter used for catheterization (including size), position, and time for start of catheterization is noted
- Residual volume (PVR) (bladder scanner) (three measurements)
- Post-catheterisation dipstick test for haematuria, leukocyturia and Specific gravity
- Scheduling Visit (V2), after Baseline Visit (V1) (within visit window)
- Complete eCRF

Visit 2 (V2):

NB! Ask for change in relevant medical history since last visit. The subject should not have changed their medication the last 24 hours before V2 or show symptoms of UTI (assessed by investigator). If signs of UTI, they must be rescheduled and registration of AE. The position used for the HCP catheterisation must be the same as the position at visit 1.

- Review of Adverse events/Serious adverse events/Adverse device events, Device deficiencies and Protocol Deviations
- Review of changes in concomitant medication
- Information regarding menstrual cycle
- Pre-catheterization volume measured in triplicate with a bladder scanner. All measurements must be above 150 ml to proceed
- Catheterisation with 2nd randomly assigned product (by HCP)
  - **NB!** HCP should count to 3 sec. if suspicious of a flow-stop before rotating the catheter to make it more clear on the profile.

- Catheterization profile (urine volume + number of flow stops)
- Volume at 1st flow stop and post catheterization volume noted from scale
- Number of flow stops noted
- Catheter used for catheterization (including size), position, and time for start of catheterization is noted
- Residual volume (PVR) (bladder scanner) (three measurements)
- Post-catheterisation dipstick test for haematuria, leukocyturia and Specific gravity.
- DK only: Subjects will be asked to perform an additional self-catheterization at site after fluid intake
  - Pre self-catheterization volume measured in triplicate with a bladder scanner. All three measurements must be above 150 ml to proceed.
  - Post self-catheterization measure residual volume with triplicate bladder scan.
  - Catheterization position noted [Sitting/standing]
  - Catheter used for catheterisation noted, including size

- Subjects are asked to assess any level of discomfort on the visual analog scale (VAS). VAS scores are asked to be rated immediately after withdrawal of catheter.
    - during catheter insertion
    - during emptying of bladder
    - at the end of emptying
    - at withdrawal of catheter

- Termination
- Complete eCRF

Unscheduled visit/call
If an unscheduled call/visit is needed the unscheduled form in the eCRF must be completed.

7.3. Flow-chart

Table 1 chart showing the connection between visits and assessments.

Visit(V)	**V0**	**V1**	**V2**
Timing of visit (Weeks)	0	0	1-7 days after V1
Activity			
Introduction to investigation and review of Subject Information Form/Informed Consent Form	X		
Signed Informed Consent		X	
Allocation of subject number		X	
Check of in- and exclusion criteria	X	X	
Pregnancy test (urine dipstick) – for subjects of childbearing potential only		X	
Baseline information		X	
Information regarding menstrual cycle		X	X
Perform device accountability		X	X
Catheterisation by HCP		X	X
Bladder scan before and after catheterization		X	X
Recording of catheterization profile (data box)		X	X
Urine volume at 1st flow stop (scale)		X	X

Number of flow-stop episodes counted by HCP		X	X
Urine volume post catheterization (scale)		X	X
Position, catheterisation start time and catheter registered		X	X
Post catheterisation dipstick for haematuria, leukocytes, and specific gravity		X	X
Self-catheterisation (DK only)			X
Triplicate bladder scan before to ensure minimum 150ml			X
Position and catheter registered			X
Triplicate bladder scan after to measure residual volume			X
Subject to complete discomfort on VAS			X
Assessment of subject's wellbeing and compliance with CIP		X	X
Concomitant medication potentially affecting urinary function (assessed by investigator) and pain management		X	X
AEs/ADEs/SAEs/SADEs		X	X
Device deficiencies		X	X
Protocol deviations		X	X
Complete eCRF		X	X
Termination form			X

7.4. Case Report Forms

All assessments and observations throughout the investigation for each subject must be carefully recorded in an electronic CRF (eCRF).

CRFs will be filled in by the principal investigator and/or delegated site personal, who have signed the Site Personnel Signature and Delegation List and Clinical Investigation Training Log.

The delegated site personal will be required to complete e-learning prior to system access. Delegated personal will receive credentials.

It is the responsibility of the principal investigator that all data are entered promptly and correctly.

7.5. Concomitant treatment

Concomitant medication, potentially affecting urinary function (assessed by investigator) and pain management, 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 visit 1 and 2. Any changes in medicine potentially affecting urinary function (assessed by investigator) and pain management, should be recorded under concomitant medication.

8. Risk – benefit analysis and ethical considerations

8.1. Risk-benefit analysis of the investigational device

A risk management process has been performed in accordance with the requirements stated in ISO 14971:2019 and in accordance with internal Coloplast procedures, including design verification, validated test methods, risk analysis and completion of a biological evaluation report for the investigational device.

Risks have been proven minimized or eliminated through appropriate risk control measures, confirmed by preclinical bench, laboratory, and biological safety evaluations.

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

- Urinary tract infection. The subject is instructed to contact the investigator/designee, if the subject experience any symptoms or signs of a new UTI.
- Mild pain or bleeding. If discovered, this must be discussed with the investigator/designee.

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

8.2. Risk-benefit for subjects participating in the clinical investigation

The investigation is conducted in accordance with current law and applicable standards, see section 15. 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 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, investigator/designees 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 17.2).

For further information on Adverse Events for this study please refer to section 18.

8.3. 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.

8.4. 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.

9. Monitoring Plan

The sponsor is responsible for ensuring appropriate monitoring of the clinical investigation activities.

The monitors will be the primary contact for the principal investigator and clinical investigation site personnel.

The monitoring of this Clinical Investigation can be delegated by the sponsor to a Clinical Research Organisation (CRO) or Clinical Research Associate (CRA). 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 extend 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 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 data are accurate, complete and verifiable from source documents and that conduct of the investigation complies with the approved CIP, subsequent amendments (if any), ISO14155:2020 and the applicable regulatory requirements.

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 directs access to subjects' files, to ensure thorough monitoring.

The investigation can 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 on site or as remote visits will be performed during the investigation:

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

9.1.1. Site selection visit

Depending on the prospective clinical investigation sites 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 if the principal investigator is known to the sponsor.

9.1.2. Initiation visit

All clinical investigation sites will complete an initiation visit during which full training on all aspects of the clinical investigation will be provided.

Training in use of the equipment used for measuring endpoints will be performed at sites.

9.1.3. Monitoring visit(s)

The sponsor shall determine the extent and nature of monitoring appropriate for the clinical investigation based on the risk assessment. The sponsor shall ensure, through oversight of the clinical investigation and timely adverse event reporting, that unanticipated adverse device effects are identified and investigated rapidly so that, where necessary, additional risk control measures can be implemented.

The site dedicated monitor is to ensure adherence to the clinical investigation plan, the safety of the subjects, accurate data recording on the eCRFs and to monitor recruitment rates and adherence to follow-up schedules. During the clinical investigation, monitors shall check that appropriate written informed consents have been obtained. The principal investigator shall permit and assist the monitor to carry out verification of completed e-CRFs against data in the source documents.

The principal investigator can delegate tasks to his/her collaborators, however the roles and responsibilities as time period of involvement for each clinical site personnel must be documented on the Site Personnel signature and Delegation list as well as training received before getting involved with the clinical investigation must be documented in the Clinical Investigation Training Log.

The monitor shall inform the sponsor about any problems relating to facilities, technical equipment or medical staff at the clinical investigation site. 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.

The monitor shall make written reports to the sponsor, including documentation of any deviations after each visit and provide written follow up action items if any, to the principal investigator and/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 firs subject in the investigation. A final monitoring visit will be performed after all subjects on site have completed the investigation.

9.2 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 eCRF 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

9.3 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.

10. Statistical considerations

10.1. Statistical design, methods, and analytical procedures

The primary objective will be evaluated by analysing the primary endpoint, supported by the secondary endpoint of flow-stop, and the secondary objective will be evaluated by analysing the secondary endpoints of adverse events and discomfort.

Baseline assessments and endpoints will be reported by descriptive statistics and/or listed.

Summaries will be presented by device i.e., investigational and comparator device and if relevant, by other grouping variables i.e., HCP and self-catheterisation.

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 9.4/Enterprise Guide version 7.1).

10.2. 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 included and hence not randomised.

- The Safety population will constitute all subjects included i.e., subjects who have given informed consent and fulfils the in- and exclusion criteria.
- 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, the primary endpoint will also be analysed in the PP population, whereas adverse events and device deficiencies will be assessed in the safety population.

10.3. Analysis of the primary endpoints

Residual volume at first flow-stop, will be analysed in a linear mixed model (LMM) 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.

The model will include following fixed effects.

- Visit (Visit 1 and 2 of catheterisation)
- Device (comparator and investigational device)

The primary endpoint will be evaluated with the null hypothesis being rejected at a 5% significance level (alpha 0.05).

Analysis of sensitivity

- The primary analysis will furthermore be analysed in the PP population, where subjects have received treatment as per protocol.

- Also, a Wilcoxon signed rank test will be applied the primary analysis, under the assumption of data not being normally distributed.

10.4. Analysis of secondary endpoints

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

- Average residual volume post catheterisation and discomfort will be presented with Descriptive statistics for a continuous variable (N, Mean, SD (standard deviation), Median, Min and Max.)

10.5. Analysis of safety data

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

10.6. Sample size

Input for the sample size calculations i.e., means and standard deviations are based on three exploratory studies CP322, CP323 and CP324. The studies investigated earlier prototypes of the micro-hole 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 60 subjects with a power of ~ 90%, assuming a difference of 15 mL, a sdcomparator of 50 mL and a sdactive of 15 mL (please see Table 10-1).

Table 10-1 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
25 (50)	10 (15)	0.05	71.9 %	40
25 (50)	10 (15)	0.05	81.2 %	50
25 (50)	10 (15)	0.05	87.7 %	60
25 (50)	10 (15)	0.05	92.2 %	70

Taken into consideration a discontinuation of 20%, the endpoint of RV1 is sufficiently supported by randomizing at least 72 subjects.

If the number of subjects contributing to the primary analysis is less than 60 subjects, it must be carefully considered to include additional subjects (subjects replaced), to maintain sufficient power in the primary analysis.

10.1. 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.

10.2. Pass/fail criteria

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

11. Data management

Data management and the final statistical analyses of all measurements described in this protocol are carried out by the Clinical Strategies team, Coloplast A/S.

Data will be collected through an electronic data capturing (EDC) system on electronic Case Report Form (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 section.

The EDC system used is Rave EDC, version 2022.3.0, 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 data management system has restricted role-based access control. The principal investigator or delegate an CRA must be trained in the system prior to getting access. The sponsor will be responsible for training the principal investigator or delegate, in completion of the eCRF. 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. The data manager will also demonstrate the system on a virtual meeting. 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 section.

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

The principal investigator, using his/her personal login information, shall sign each eCRF before the database can be locked. This must be done after approval from the data management team.

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

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 Validation Plan describes which edit checks, range checks, and other consistence checks that will be done on the clinical data during conduct of the investigation. The Data Validation Plan will be developed in collaboration with the Clinical Manager and the Statistician and will be aligned with the monitoring section.

Principal Investigator, or delegate, at the clinical site will perform primary data collection directly into the eCRF or drawn from source-document (i.e., medical records or notes) 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 principal 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 principal 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. This deadline will be shorter after LPO at the site, and will be agreed with the monitor.

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

11.1. Data collection procedure

During HCP catheterisations at visit 1 and 2 a catheterisation profile is created using a scale connected to a data box. The catheterisation profile shows a scale curve of accumulated urine (urine volume/time). The catheterisation profiles are analysed by two Coloplast specialists, independently, and results then compared to derive the relevant endpoints. The data for the catheterisation profile relevant endpoints are then uploaded to the database by the data management specialist.

Discomfort will be assessed using the visual analog scale (VAS). The subject will be asked to indicate the level of discomfort (from 'No discomfort' and 'Worst possible discomfort') in a 10 cm line on paper. Hereafter, the site personnel must measure the length (cm) from the start of the line to the subject's mark and add to the paper form. In addition, the site personnel must register the number in the eCRF.

The remaining endpoints, assessment, backup measurements and baseline information can be entered directly into the eCRF.

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

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

The principal 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.

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

11.2. Data retention

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

12. 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 EC and applicable regulatory authority. Substantial changes may require approval from the EC and applicable regulatory authority prior to implementation.

13. 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 EC and CA approved investigation plan.

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 Site Report – Periodic Monitoring 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

14. Device Accountability

All access to the investigational devices (including comparators) 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 PI or an authorized designee keeps records documenting the receipt, use and return and disposal of the investigational devices, which includes:

- Date of receipt.
- Identification of each investigational device (batch no./serial no./unique code).
- The expire date.
- The date(s) of use.
- Subject identification.
    - The date on which the investigational device was returned/explanted from the subject
    - The date of return unused, expired or malfunctioning investigational devices

15. Statement of compliance

The clinical investigation is conducted in accordance with:

- Ethical principles that have their origin in the Declaration of Helsinki, 1964, Last amended at the 59th WMA General Assembly, 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.

15.1. 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.

15.2. 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 product 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)l 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 products 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 [redacted] 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 [redacted] 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

15.3. Indemnity

All subjects are fully covered by Coloplast A/S insurance throughout the investigation.

15.4. 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.

16. 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, *all anticipated adverse device effects* and then have a minimum of *24h (ensure ample time)* 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.

17. Subject compensation

17.1. Compensation in case of injury

Product 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.

17.2. Compensation for participating in the clinical investigation

This is to compensate for any inconvenience caused during the conduct of the study catheterisations and 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.

18. Adverse events, adverse device effects and device deficiencies

18.1. 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 or not 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.

18.2. Adverse device effect

An adverse event, which is related to the use of the investigational medical device (including comparator), 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 1 lists anticipated adverse device effects that may occur.

Table 1 Anticipated adverse device effects and their likely incidence rates

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

18.3. 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.

EXAMPLES OF DEVICE DEFICIENCY
No coating on investigational device
No micro-holes
Broken packeting
Broken catheter

18.4. 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.

18.4.1. 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.

18.4.2. Anticipated serious adverse device effect (ASADE)

There are no ASADE.

18.4.3. 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.

18.5. 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 8.2). 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.

18.6. Reporting and timelines

18.6.1. 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 Coloplast investigational product 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

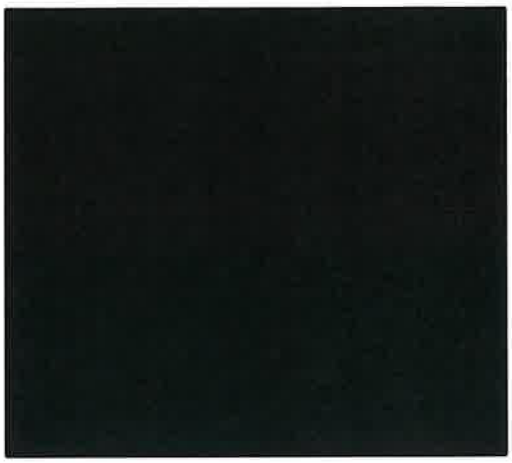
- **Not related**, the event has no temporal relationship with the use of the test material or the procedures.
- **Unlikely related,** the relationship with the use of the test material seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be 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 were 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.

Please report to:



18.6.2. 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).

19. 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/IRB. 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/IRB about the termination of the site.

20. 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 must be submitted to EC and regulatory authorities.

21. 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.

22. 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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