Clinical Investigation Plan

CP341

Exploratory study investigating the acute effect of intermittent catheterisation on the bladder mucosa of healthy volunteers with a micro-hole zone catheter compared to a conventional 2-eyelet catheter.

Investigation period: December 2021 - March 2022

Document date: December 13 2021

CHANGE LOG

VERSION NUMBER	ISSUED BY *(INITIALS)*	COMMENTS (MAJOR CHANGES SINCE LAST REVISION)
1.0	[redacted]	Initial document created based on template
2.0	[redacted]	Correct units for WBC and RBC labs.
3.0	[redacted]	Updates to the endpoints and statistical sections.

SYNOPSIS OF THE CLINICAL INVESTIGATION

Title

CP341 / Exploratory study investigating the acute effect of intermittent catheterisation on the bladder mucosa of healthy volunteers with a micro-hole zone catheter compared to a conventional 2-eyelet catheter.

Test Product and Comparator:

The female test catheter is based on the current SpeediCath™ standard female catheter. The SpeediCath™ catheter has two oval holes by the tip used for voiding while the test catheter has a micro-hole zone comprising of a number of smaller holes by the tip, creating a draining zone. The hole punch process used for SpeediCath™ Standard, has been exchanged with a laser process to accommodate for the smaller hole size.

Hence, non-US approved test products will be investigated. The test product will be provided by Coloplast A/S, Denmark.

The comparator product is the Infyna Chic™ (Hollister) catheter, which is considered Standard of Care. The comparator product will be supplied by Coloplast A/S, Denmark.

Intended Purpose

The test product is a urinary catheter for bladder drainage through the urethra. The product is for intermittent use.

Aim and Objective(s)

The overall purpose of the clinical investigation is to explore the effect of micro-hole zone versus conventional catheter eyelets on bladder mucosa during catheterisation.

The primary objective is to show that a micro-hole zone catheter (MHC) causes fewer endoscopically noticeable epithelial and vascular changes in the bladder mucosa during catheterisation compared to a conventional 2-eyelet catheter (2EC).

Design of the investigation

This investigation is a randomized, single-blinded, parallel, single-center investigation. In total, up to 50 subjects (40 completers) will be included and each subject will have two test visits overseen by the Principal Investigator (PI), or designee. Each subject will be enrolled in the investigation, which can be up to 3 days (if Day 0 and Day 1 are not on same day). The subjects will be randomly assigned to test either the test product or the comparator product, with at least 20 subjects assigned to each product."

Expected duration of the clinical investigation:

The investigation will be conducted from November 2021 through February 2022.

Endpoints & Assessments:

Primary endpoint:

- Change in appearance of the bladder mucosa (pre- and post-catheterization) (Δ), rated on a 4-point scale following visit 2.

Exploratory endpoints:

- Haematuria red blood cell count (RBC) at visit 2.
- White blood cell count (WBC) at visit 2.

Assessments

- Visual blood at cystoscopes and catheter – Yes/No
- Pre-catheterization residual volume (ml)
- Haematuria red blood cell count (RBC)
- White blood cell count (WBC)

- Urine volumes (mL)

Safety assessments:

- Adverse events
- Device deficiencies
- Concomitant medications

Population/subjects

A total of 50 subjects (healthy female volunteers) will be recruited in order to secure inclusion, randomization and completion of at least 40 subjects, assuming an approximate drop-out rate of 20%." The subjects will be recruited from a single center, American Health Research (AHR).

Inclusion/Exclusion Criteria:

To be included in the investigation a subject must comply with the following inclusion criteria:	Justification for inclusion criteria
1. **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.
2. **Is at least 18 years and have full legal capacity**	To meet the Helsinki Declaration
3. **Is female**	The product is indicated for use with females
4. **Has a negative urine Multistix dipstick test for erythrocytes (haematuria)**	Haematuria could be a sign of urinary tract infection (UTI).

A subject is not allowed to participate in case he/she:	Justification for exclusion criteria:
1. **Has used an internal urinary catheter or cystoscopy within the past month**	To reduce potential bias from other events non-distinguishable from this study
2. **Has prior history of bladder surgery**	To reduce potential bias from other events non-distinguishable from this study
3. **Is symptomatic and/or on medication for overactive bladder**	To reduce potential bias from other events non-distinguishable from this study
4. **Has evidence of ongoing, active, symptomatic UTI (assessed by PI, or delegate)**	To reduce potential bias from other events non-distinguishable from this study
5. **Is pregnant and/or breast-feeding**	To reduce potential bias from other events non-distinguishable from this study
6. **Is participating in other clinical investigations during this investigation**	To reduce potential bias from other events non-distinguishable from this study
7. **Is menstruating during study period**	To reduce bias of the RBC analysis.

Investigation approval

This investigation is a non-significant risk study and will be approved by the Institutional Review Board (IRB) before initiation.

LIST OF ABBREVIATIONS

ABBREVIATION	WRITTEN OUT	EXPLANATION
2EC	2-eyelet catheter	
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	
DD	Device deficiency	
eCRF	Electronic Case Report Form	
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	
MHC	Micro-hole zone catheter	
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	
RBC	Red Blood Cell Count	
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	
WBC	White Blood Cell Count	

SIGNATURE PAGE

All parties declare by their signature on the electronic or the separate signature page to follow the Clinical Investigation Plan CP341 in accordance with the Declaration of Helsinki, ISO 14155, and FDA Regulations.

TABLE OF CONTENTS

1 List of personnel involved in the Investigation

1.1 Sponsor Representatives

Coloplast A/S, Holtedam 1-3, 3000 Humlebæk is the Sponsor in this clinical investigation.

SR. CLINICAL MANAGER	STATISTICIAN
[redacted]	[redacted]
MEDICAL AFFAIRS PROJECT MANAGER	**DATA MANAGEMENT SPECIALIST**
[redacted]	[redacted]
DIRECTOR OF CLINICAL STRATEGIES	**DIRECTOR OF CLINICAL OPERATIONS**
[redacted]	[redacted]
MEDICAL ADVISOR	**SR. MEDICAL WRITER**
[redacted]	[redacted]

1.2 Site Personnel

This clinical investigation will be conducted in the United States at a single-center, American Health Research, AHR.

The Clinical Manager is responsible for maintaining an updated list of all sites and personnel in the sponsor electronic trial master file (eTMF). Qualified site personnel can perform investigational related tasks per the Principal Investigator's (PI) delegation. This delegation must be documented in the 'Site Personal Signature and Delegation List' for each site. All PIs and designees will receive training in all aspects of the investigation and before they can begin any study related procedures.

1.3 Clinical Research Organizations

A Site Management Organization (SMO) will be used to help conduct the investigation as a clinical site. All sponsor representatives' roles and responsibilities will be listed on the 'Site Personnel and Contact Details List'.

1.4 Other Vendors

The data management system is delivered by Medidata Solutions and is named Rave. Current version number is version 2020 3.2. The system is designed for electronic data capture, and it is compliant with the requirements of 21 CFR part 11.

2 Rationale for conducting the clinical investigation

The hypothesis is that a catheter with multiple micro-holes will cause less mucosal suction through the eyelets during bladder emptying compared to a conventional 2-eyelet catheter and that suction can cause epithelial and vascular changes in the bladder mucosa.

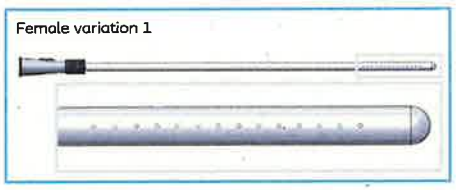
3 Objective(s) of the clinical investigation

The overall purpose of the clinical investigation is to explore the effect of micro-hole zone versus conventional catheter eyelets on bladder mucosa during catheterisation. The primary objective is to show that MHC cause fewer epithelial and vascular micro-trauma in the bladder mucosa during catheterisation compared to a 2EC.

4 Investigational Products

4.1 Description of Test Product

The female test catheter is compositional identical to the 510K cleared (K180258) SpeediCath™ standard female catheter. The SpeediCath™ catheter has two oval holes by the tip used for voiding while the test catheter has a micro-hole zone comprising of a number of smaller holes by the tip, creating a draining zone. The hole punch process used for SpeediCath™ Standard, has been exchanged with a laser process to accommodate for the smaller hole size.



No of rows:	4
Hole size:	0,4mm
Distance between holes:	2,1mm
No of holes:	14x4

Hence, non-US approved test products will be tested. The test product will be provided by Coloplast A/S, Denmark.

4.2 Comparator

The comparator product is the Infyna Chic™ (Hollister) catheter, which is considered Standard of Care. The comparator product is already on the market and will be used within the intended purpose in this clinical investigation. The comparator will be supplied to the site by Coloplast A/S, Denmark.

4.3 Manufacturing

The Test Products will be manufactured at Coloplast A/S, Holtedam 1-3, 3050 Humlebæk, Denmark.

The comparators are manufactured by Hollister.

4.4 Identification and traceability of the investigational products

All investigational products (test and comparator products) are labelled as per regulations and include "CAUTION – Investigational device. Limited by United States law to investigational use" on the label. The products are also identified with study number, product name/code, and item/lot number and accounted for through a master sponsor accountability log. Upon IRB approval, investigational products will be shipped to the principal investigator, or designee. Additionally, all investigational products will be accounted for and documented on a site accountability log. The receipt and disposition of all investigational products will be verified through monitoring. All unused products will be returned to Coloplast at the end of the study.

4.5 Intended use of the test product in the clinical investigation

The test product is a urinary catheter for bladder drainage through the urethra. The product is for intermittent use.

4.6 Intended population for the test product

The test product is indicated for use with adults.

4.7 Handling of the investigational products

The handling of the investigational products is described in detail in the Instruction for Use (IFU), which is included in all boxes with the products. It is stated in the IFU that the investigational products are for single-use and must be kept away from direct sunlight. Reprocessing, washing, disinfection, and sterilisation may compromise product characteristics, causing additional risk of physical harm to or infection of the user.

All site personnel will receive training by the sponsor and/or principal investigator in the handling and correct use of the investigational products.

For further details regarding the test product, please refer to the Investigators Brochure.

4.8 Total number of investigational products intended for the clinical investigation

The subjects will be included for up to 3 days. Subjects will undergo 1 catherization and expect to use up to 1 catheter.

5 Design of the clinical investigation

5.1 General

A randomized, single-blinded, parallel study, in which each subject will undergo one catheterization comprising of 6 cycles of filling and emptying the bladder. Each cycle will comprise of filling the bladder with 250mL of saline liquid (50mL/min) through the catheter, followed by bladder emptying through the catheter. The catheter will be rotated during emptying at each occurrence of a flow-stop to release any mucosal suction, with the MHC or 2EC, depending on randomization. To ensure that all catheters are rotated at some point during drainage, every catheter should be rotated after complete emptying. Subjects shall be sitting or standing for the catheterization and filling/emptying cycles to increase the efficiency of drainage.

Upon first insertion of the catheter, the residual volume pre-catheterization will be recorded to ensure minimal residual urine left in the bladder prior to the 6 cycles.

The effect of the micro-hole zone or conventional eyelets on the epithelial and vascular urothelial tissue will be assessed with cystoscopies before and after the catheterization including 6 cycles of filling/emptying/rotating.

One investigator will perform the cystoscopies, catheterizations, and make initial assessments of the cystoscopy images according to a 4-point rating scale as described in 5.3. Two additional investigators will evaluate the endoscopic images post-procedure in a blinded fashion. The evaluations by the 3 investigators will be compared.

The urine at pre- and post-catheterization at Visit 2will be collected for each subject, the total volume noted, and the container will be sent to a local lab for examination of microscopic RBC[1] and WBC results.

Each visit will take approximately 1-2 hours to complete.

Figure 5-1 presents the study overview and Table 7-1 presents the schedule of assessments.

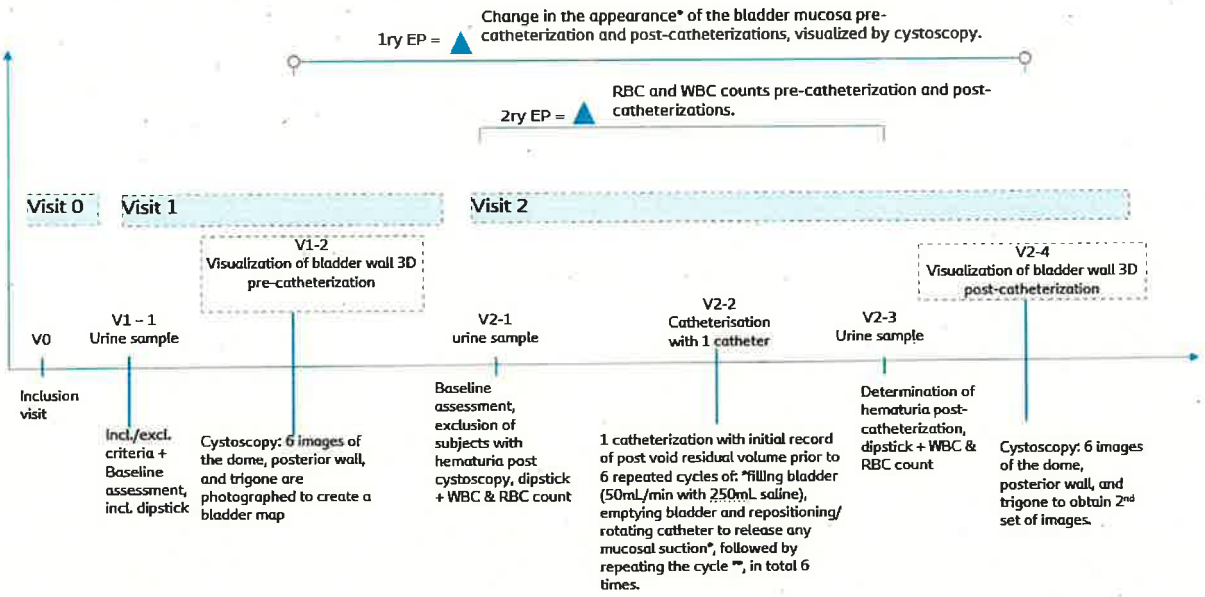


Figure 5-1 Study overview

5.2 Investigation Endpoints

Endpoint details are included in the schedule of assessments. See section 7.4.

5.2.1 Primary endpoint

- Change in appearance of the bladder mucosa post- and pre-catheterization (Δ), rated on a 4-point scale 1) no lesions evident; 2) minor mucosal and blood vessel lesions; 3) major blood vessel lesions, and 4) major mucosal and blood vessel lesions, following visit 2

5.2.2 Exploratory endpoints

- Haematuria red blood cell count (RBC) at visit 2
- White blood cell count (WBC) at visit 2.

5.2.3 Assessments

- Visual blood at cystoscopes and catheter – Yes/No
- Pre-catheterization residual volume (ml)
- Haematuria red blood cell count (RBC)
- White blood cell count (WBC)
- Urine volumes (mL)

5.2.4 Safety assessments

- Adverse events
- Device deficiencies
- Concomitant medication

5.3 Rationale for selection and measurement of endpoints

Bladder lesions will be assessed with a cystoscope and graded by the principal investigator during the procedure, followed by a post-procedure evaluation of the images by two other specialised investigators in a blinded fashion.

Lesions are based on change in appearance of the bladder wall mucosa before and after catheterisation graded on a 4-point scale: 1) no lesions evident; 2) minor mucosal and blood vessel lesions; 3) major blood vessel lesions, and 4) major mucosal and blood vessel lesions. The change in the appearance of the bladder mucosa will be calculated by the difference between the grading of bladder lesions pre-catheterisation and post-catheterisations.

Figure 5-2 presents examples of changes in bladder mucosal grade observed pre- and post-drainage, from Grocela et al. 2010[2].

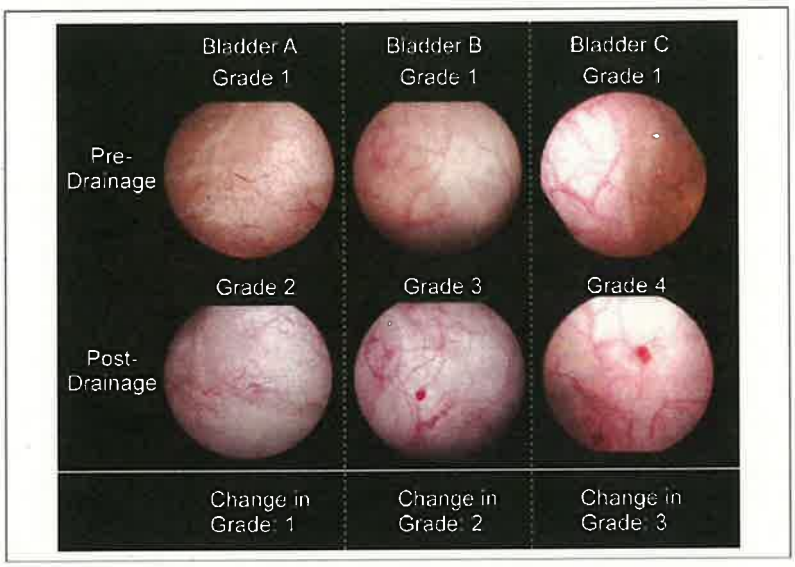


Figure 5-2 Examples of changes in bladder mucosal grade observed pre- and post-drainage, from Grocela et al. 2010[2]

RBC and WBC before and after catheterisation will serve as exploratory endpoint.

5.4 Demography and potential compromising factors

The following baseline data will be collected and registered at Visit 1 by the investigator or designee:

- Date of Informed Consent
- Subject number
- Date of visit
- Age
- Check of inclusion criteria
- Check of exclusion criteria
- Complete randomization

There are no restrictions. However, concomitant medication should be noted. Prophylactic antibiotics should be provided as one time treatment at first visit.

5.5 Equipment

The Ambu® aScope™ 4 Cysto is the cystoscope which will be used in this investigation. The aScope™ 4 Cysto is a sterile, single-use, flexible cystoscope intended to be used for endoscopic access to and examination of the lower urinary tract.

The Ambu® a View™ 2 Advance is a display unit used in conjunction with the cystoscopes in order to view the cystoscopy procedure.

5.6 Randomisation Procedure

All subjects that meet the eligibility criteria will be randomised to one of two treatment arms, the test product, or the comparator. Randomisation will be centralized using Medidata RAVE.

5.7 Blinding

Subjects will not be blinded during this investigation, as it is not possible to blind the products due to visible differences. The two investigators conducting the cystoscopy reviews will be blinded. The images will be de-identified and uploaded to a secure site. The images will be identified with a subject number, date, and time. The investigators will be provided access to the secure site for their review. Each investigator will grade both the post-catheterization image and pre-catheterization image, i.e., from the same location (grading is done in a comparative manner).

Any discordant gradings will be adjudicated amongst the investigators.

Additionally, the trial statistician will be blinded until database lock to ensure decisions related to data before database lock do not affect final results.

5.8 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 IRB will be notified.

- First subject enrolled (November 2021).
- Last subject completed (January 2022).
- Database Lock (February 2022).

Each subject participation will be approximately 3 days.

6 Clinical Investigation population

According to the sample size calculations (see section 10.4) 40 subjects are required to complete the study with measurements of the primary endpoint. Considering a drop-out rate of 20%, the required total number of subjects to be enrolled in the trial shall be 50. The subjects will be enrolled at one site in the United States.

6.1 Eligibility criteria

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

6.1.1 Inclusion criteria

To be included in the investigation a subject must comply with the following inclusion criteria:	Justification for inclusion criteria
1. **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.
2. **Is at least 18 years and have full legal capacity**	To meet the Helsinki Declaration
3. **Is female**	The product is indicated for use with females
4. **Has a negative urine Multistix dipstick test for erythrocytes (haematuria)**	Haematuria could be a sign of blood in urine infection.

6.1.2 Exclusion criteria

A subject is not allowed to participate in case he/she:	Justification for exclusion criteria:
1. **Has used an internal urinary catheter or cystoscopy within the past month**	To reduce potential contamination from other events non-distinguishable from this study
2. **Has prior history of bladder surgery**	To reduce potential bias from other events non-distinguishable from this study
3. **Is symptomatic and/or on medication for overactive bladder**	To reduce potential bias from other events non-distinguishable from this study
4. **Has evidence of ongoing, active, symptomatic UTI (assessed by PI, or delegate)**	To reduce potential bias from other events non-distinguishable from this study
5. **Is pregnant and/or breast-feeding**	To reduce potential bias from other events non-distinguishable from this study
6. **Is participating in other clinical investigations during this investigation**	To reduce potential contamination from other events non-distinguishable from this study
7. **Has menstrual bleeding during study period**	To reduce bias of the RBC analysis.

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 to ensure the subject is not pregnant. The urine pregnancy test will be performed by dipstick at the trial site. Furthermore, the female subjects should not be breastfeeding, when participating in the clinical investigation.

6.2 Subject Recruitment & Screening

The recruitment of potential subjects will commence only when IRB approval is received. Recruitment will occur in the United States at the single-center, American Health Research (AHR). The recruitment period from first subject enrolled to last subject enrolled will be approximately 2 months. The recruitment process will be conducted through site screening and advertisement.

6.2.1 Screening Potential Subjects

If a subject is eligible and interested in participating, then written information about the investigation (subject information) will be provided to the subject to ensure they are given the opportunity to understand what the investigation is about. Subjects will be given plenty of time to have any questions they may have addressed by the investigator, or designee. The subject information provides information to subjects about how to contact the investigator or a representative thereof, or a representative of the sponsor (name, telephone number and e-mail address), if they wish to learn more about the study.

If an eligible subject is interested in participating after they have had time to review the subject information, a screening visit will be arranged. This visit will be done in a quiet room reserved to ensure privacy at the investigator's clinic/office. When arranging the visit, the subject must have received the Information Form and given adequate time to review it. The subject will receive both written and verbal information about the possibility of bringing a companion to the visit and to any possible subsequent visits.

The subject has the right to wait before deciding to participate. If/when the subject decides to participate, he/she will be asked to sign the informed consent form. If a subject so desires, and it is certain that it is understood what the investigation entails, and the relevant forms have been signed, the subject is considered enrolled in the investigation.

The Coloplast clinical manager will have close contact to the site during the recruitment period. The principal investigator, or designee, will notify the clinical manager when a subject is enrolled and all future planned visits.

6.3 Point of Enrollment

A subject is considered enrolled in the investigation when written informed consent is obtained. The expected duration for each subject is described in section 5.8.

6.4 Subject Screening and randomization Failures

Subjects that have signed the informed consent form but fail to comply with the eligibility criteria are considered screening failures. A screening failure can be replaced by a new subject if the new subject can complete the investigation within timelines (before last subject last visit and within visit windows).

6.5 Subject Withdrawal Criteria

The subject can withdraw from the investigation at any time for whatever reason without any consequences for their future treatment outside the clinical investigation. The Investigator may also withdraw a subject from the investigation at any time if s/he judges 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.
- 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.

6.6 Subject Identification and Confidentiality

Subjects will be identified on the electronic CRF (eCRF) and any other document transmitted to the sponsor by the principal investigator, or designee, by a unique identification number (subject number) only.

Data entered on the eCRF are confidential and will only be available to the sponsor (including sponsor delegates), members of data management teams, the statistician, or Medical Advisor and if requested to regulatory authorities.

The principal investigator will maintain, as part of the investigator site file, a list identifying all subjects entered in the clinical investigation (Subject Identification Code and Enrolment List). This list is confidential to all others than the Principal Investigator, or designee at the site.

7 Procedures

7.1 Clinical investigation-related procedures

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

See section **Error! Reference source not found.** for an overview of the clinical investigation-related procedures during subject visits, telephone visits, and at product/baseplate change.

7.2 Subject Visits

7.2.1 Screening/Baseline Visit (Visit 0)

If a potential subject is interested in participating after the first contact, a visit (visit 0) will be arranged in a room reserved to ensure privacy and quiet surroundings at the investigator's clinic/department. When arranging the visit, it will be ensured, that the subject has received the Subject Information Form and given plenty of time to review it. The subject will receive both written and verbal information to ensure that the subject understands what was read and explained and can freely agree to participate in the investigation. The subject will, beforehand, also be informed about the possibility of bringing a companion to any subsequent visits. During the visit, the Principal Investigator or designee will provide oral information about the investigation based on the Subject Information Form. The subject has the right to wait before deciding on participation.

If/when subjects decide to participate, they will be asked to sign the Informed Consent Signature Form. If a subject so desires, and it is certain that it is understood what the investigation entails, and the informed consent form has been signed, the subject is considered enrolled in the investigation. Enrolled subjects are entered in the electronic data capture system and will be randomised to either catheterization with MCH or with 2EC. If a subject is enrolled and does not meet inclusion/exclusion criteria, they will be deemed screen failures and will not be randomized.

It is preferred that Visit 0 and Visit 1 are performed on the same day as the urine sample applied for inclusion or exclusion will also be used to determine RBC and WBC at baseline prior to cystoscopy (see flowchart in Table 7-1).

Once consented, the subject will be allocated a subject number.

7.2.2 Study visits (V1, and V2)

NOTE: All urine volumes (including pre-catheterization residual volumes) will be measured in the same manner throughout the study.

Day 1 (Visit 1):

- Evaluation of Inclusion/Exclusion criteria, including the assessment of any ongoing, active, symptomatic UTI (assessed by Investigator)
- Collection of demographic and baseline data

- Randomisation
- V1-1: A baseline urine sample pre-cystoscopy is collected for the following examination:
    - Dipstick for pregnancy (positive/negative)
    - Dipstick for haematuria (positive/negative)
        - Negative
            - Negative
            - Non-haemolysed 10Ery/ul (+/-)
            - Haemolysed 10Ery/ul (+/-)
        - Positive
            - Non-haemolysed 80 Ery/ul (2+)
            - Haemolysed 25 Ery/ul (1+)
            - Haemolysed 80 Ery/ul (2+)
            - Haemolysed 200 Ery/ul (3+)

- V1-2: The 1st cystoscopy is performed, where the scope is positioned at the centre of the bladder and 6 adjacent images of the dome, posterior wall, and trigone are filmed/photographed to create a naïve bladder map. Cystoscope is inspected for visual blood.
- Collection of concomitant medications. ***Prophylactic antibiotics should be provided as one time treatment at first visit.***
- Collection of adverse events, if applicable

Day 2 (Visit 2):

- V2-1: Urine from a natural void will be collected pre-catheterization. Once the urine sample is obtained, urine volume(mL), RBC and WBC will be evaluated. Haematuria will also be evaluated via dipstick.

- V2-2: Catheterization with either a micro-hole zone- or a 2-eyelet catheter (depending on the randomization). Upon first catheter placement, residual volume pre-catheterization is recorded. Hereafter, the bladder is filled with 250mL (at intervals of 50mL/min) of saline water followed by bladder drainage via the catheter. The catheter is rotated to release any mucosal suction during emptying. Once fully emptied, the catheter is rotated once more to ensure all catheters are being rotated at some point during emptying. The bladder is again filled with 250mL (at intervals of 50mL/min) of saline water followed by bladder drainage and rotations. This procedure is repeated 6 times using the same technique and equipment. The catheter is inspected for visual blood.

- V2-3: The subject will be provided water to drink and the urine from a natural void will be collected. Once the urine sample is obtained, urine volume(mL), RBC and WBC will be evaluated Haematuria will also be evaluated via dipstick.

- V2-4: A 2nd cystoscopy is performed, where the scope is positioned at the centre of the bladder and the same 6 adjacent images of the dome, posterior wall, and trigone are filmed/photographed as during the 1st cystoscopy and a second set of images are obtained. The captured areas are to be carefully selected so they match those in the first set of photographs based on blood vessels and surface features. Cystoscope is inspected for visual blood.

- Collection of any new concomitant medications

- Collection of adverse events and/or device deficiencies, if applicable

7.3 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 2). 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 product or participation. This is to ensure that any device-related events are documented and to safeguard the subjects' health.

7.4 Schedule of assessments

Table 7-1 Schedule of assessments

	Day 0	Day 1		Day 2			
Procedures	V0	V1-1	V1-2 (Cystoscopy)	V2-1	V2-2 (1 catheterization: 6 x repositioning)	V2-3	V2-4 (Cystoscopy)
Informed consent (Allocation of Subject Number in EDC)	X						
Inclusion/Exclusion criteria		X					
Randomization		X					
Demographics & Baseline Data Collected		X					
Urine sample -Dipstick haematuria -Dipstick pregnancy test *(pregnancy test only at V1-1)*		X		X		X	
RBC				X		X	
WBC				X		X	
Cystoscopy Imaging			X				X
Bladder Assessment							X
Volume of Urine recorded				X		X	
Pre-catheterization Residual Volume					X		
Visualization of blood			X		X		X
Adverse Events	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X
Device Deficiencies					X	X	X

7.5 Concomitant Medications

Concomitant medications will be registered in the eCRF. All concomitant medications the subject has taken from the time of consent through study termination will be collected.

7.6 Prohibitive Medications/Treatments

There are no prohibitive medications in this study.

8 Risk-benefit analysis and ethical considerations

8.1 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.

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 product.

To mitigate and reduce the risks, the site personnel will be trained, according to the IFU.

The investigation is conducted in accordance with current applicable standards. Please refer to section 15, Statement of compliance. The rights, safety and well-being of human subjects shall prevail over the interest of science.

Risks have been proven minimized or eliminated through appropriate design control, confirmed by pre-clinical bench, and laboratory studies.

8.2 Risk-benefit analysis for the conduct of the clinical investigation

The participating subjects will contribute with important information for the development of new intermittent catheters, that may reduce bladder complications; specifically, mucosal microtrauma associated with the conventional eyelet catheters. Due to the actions taken to mitigate any risks, the risks and disadvantages when participating in this clinical investigation are estimated as low. The subject's health will not benefit directly from this investigation.

8.3 Delegation of responsibility

Qualified site personnel can perform investigational related tasks per the Principal Investigator's (PI) delegation. This delegation must be documented in the 'Site Personal Signature and Delegation List' for each site. All Principal Investigators and designees will receive training in all aspects of the investigation and before they can begin any investigational related tasks. The training must be documented in the 'Clinical Investigation Training Log' at each site. The Principal Investigator is responsible for maintaining these logs.

9 Monitoring

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).

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.

For this clinical investigation, the below described monitoring procedures have been determined.

The data collected throughout the investigation, and the conduct of the investigation, will be monitored per 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), ISO14155 and the applicable regulatory requirements.

The monitoring process is briefly described below and detailed in the Monitoring Plan. The monitoring will be conducted per the monitoring plan by qualified designee 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 that they require, including direct access to the subjects' files.

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 will be performed during the investigation:

- Site selection visit
- Site Initiation Visit
- Periodic Monitoring visits
- Close Out visit

9.1 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 if the Principal Investigator is known to the sponsor.

9.2 Site Initiation visit

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

9.3 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 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.

A remote, centralized review of the data entered in the eCRF, will be performed by Coloplast CM throughout the conduct of the investigation. See section 9.3.

9.4 Source data verification

A source document is a document in which data collected for a clinical investigation is first recorded. This data is usually later entered in the eCRF. Source documents are defined as "original documents, data, and records". Source documents contain source data, which is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the clinical investigation.

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 ensure 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. In some cases, 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.

Only the Principal Investigator, or designee, and the sponsor representatives will have access to all the eCRFs.

9.5 Remote monitoring

Remote or centralized monitoring is a remote evaluation 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. 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 violations 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 eCRFs 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 violations, and delays in reporting data), and clinical data to identify early on corrective actions needed for characteristics correlated with poor performance or noncompliance.

10 Statistical considerations

All baseline assessments, endpoints and other measurements will be reported by descriptive statistics and/or listed. Summaries will be presented by treatment 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.

A significance level of alpha equal to 0.05 (two-sided) is applied and due to the exploratory nature of this investigation, no procedures for multiplicity control or adjustment of error probabilities will be applied.

Adverse events will be listed and/or summarized. Device deficiencies and concomitant medication will be listed as well.

10.1 Definition of analysis populations

Intention to Treat (ITT), Safety and Per Protocol (PP) populations will be defined at a formal data review meeting before database lock. As a minimum, the data manager, the clinical manager and the statistician will be involved in the classification of subjects.

The Safety population (basis for the AE summary) will include subjects with valid informed consent.

The ITT population (Full analysis set) will be constituted by all randomized subjects, with valid informed consent, who have been exposed to at least one product, and with recorded information on at least one endpoint (non-missing).

Due to the explorative nature of this investigation, no formal PP population is planned. However, if deemed necessary, a PP population will be established, based on a subset of the ITT population.

Individual endpoints/data points may be excluded from analysis, even though the corresponding subject belongs to the ITT and/or PP population. Any exclusion of subjects or data points from any of the populations must be documented.

All analyses will be based upon the ITT population and AEs will be summarized based on the safety population.

The Safety population will include all subjects who have given informed consent.

10.2 Analysis of the primary endpoint

Change in bladder appearance (mucosa post- and pre-catheterization) translated into a grading scaled from 1-4 will be analysed in a mixed model with treatment (comparator and investigational device) as fixed effect.

Treatment differences as well as 95% confidence intervals will be estimated by using Proc Mixed in SAS.

10.3 Analysis of exploratory endpoints

All exploratory endpoints i.e., RBC and WBC will be presented by descriptive statistics.

10.4 Sample size

As this is an exploratory study no formal sample size calculation has been performed. It is assumed that a total of 40 completers i.e., 20 completers (a minimum of 18 completers needed) in each group (MHC and 2EC) will be adequate for obtaining indications on differences in eyelet associated trauma during bladder emptying with either a MHC or a 2EC.

10.5 Level of significance and power

A two-sided significance level of 5% will be applied. For a description of the power see section 10.4 above.

10.6 Pass/fail criteria

As this is an exploratory investigation with no prior experience, any result will provide valuable insight into how catheter design affects the bladder mucosa in the clinical setting.

11 Data management

11.1 Data collection and data management

11.1.1 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 2020.3.2, 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 Principal Investigator, or designee, 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 (medical records) 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 Principal Investigator, or designee, 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 5 days after the visit / procedure.

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

The cystoscope images will be uploaded to a secure environment.

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 Principal Investigator will keep a separate list of the subjects' ID numbers, enrolment date, randomisation number, date of birth, names, phone number, email and addresses in a locked room/cabinet. Only data referred to in this clinical investigation plan will be recorded in the CRFs.

11.1.2 Database Management, Queries and Quality Control

The data management system has restricted role-based access control. The Principal Investigator, or designee 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 designee, 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, or designee, 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 SOPs.

11.2 Data retention

All investigation site documents must be archived for a minimum period of 10 years after the final clinical investigation report has been signed. The monitor is responsible for informing the investigator and the CM if this period should be longer for their sites according to local regulation.

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 IRB approved investigation plan.

A minor deviation is defined as those that do not increase risk or decrease benefit or do not 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 well-being 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 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 report and any actions for additional follow up are addressed with the Investigator.

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.

Details about the deviation will be collected, for example:

- Site ID
- Subject ID
- Deviation Date
- Clear and concise description of the event
- The reason for the deviation and any corrective action taken, including the date of the corrective action.

If applicable, record the EC notification date and retrieve a copy of the EC Submission Letter for the eTMF.

14 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 investigational devices to the investigational sites until return of or disposal.

The PI, or designee, keeps records documenting the receipt, use and return and disposal of the investigational devices, which includes:

- Name of the product received
- Date of receipt
- Identification of each investigational products (batch no./lot no.)
- Number of products received
- Number of products distributed to subject
- The date(s) of use
- Subject identification
- The date on which the investigational product was returned/explanted from the subject
- The date of return unused, expired or malfunctioning investigational products to Sponsor

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.
- FDA Regulations
- ISO 14155:2020 "Clinical Investigation of medical devices for human subjects – Good clinical practices".

16 Ethics committee and regulatory authorities

The CIP and/or other relevant documents are submitted to the appropriate IRB, if applicable. This clinical investigation will not begin until the required approval from the IRB has been obtained. Any amendment to the clinical investigation plan will be submitted to the same IRB. Sponsor will notify the relevant IRB of the end of the clinical investigation.

17 Data protection

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 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 Principal Investigator, or designee). Such cases will imply a transfer of 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

17.1 Indemnity

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

17.2 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 contract.

18 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 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 designee. 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 it 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.

19 Subject compensation

19.1 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.

19.2 Compensation for participating in the clinical investigation

If applicable, subjects will be compensated for their participation in the clinical investigation.

Table 19-1 Compensation for subject participation

20 Adverse events, adverse device effects and device deficiencies

20.1 Adverse events

An adverse event is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users, or other parties, whether or not related to the medical device(s), or the procedures involved. This could include events such as headache or dizziness.

20.2 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 related or possibly related 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, or any malfunction of the medical device, as well as any event resulting from use error or from intentional misuse of the device.

20.3 Device deficiency

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

20.4 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 fetal distress, fetal death or a congenital abnormality or birth defect.

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

- Suitable action had not been taken, or
- Intervention had not been made, or
- 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.

20.4.1 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.

20.4.2 Anticipated serious adverse device effect (ASADE)

Anticipated serious adverse device effect is any event that by its nature, incidence, severity, or outcome has been previously identified in the risk analysis report.

20.4.3 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.

20.5 Medical care of subjects

Principal investigator shall ensure that adequate medical care is provided to a subject experiencing an adverse event during and after participation in the clinical investigation. All serious adverse events will be followed until a resolution is addressed.

The status of all ongoing adverse events is documented during site close-out.

20.6 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

20.7 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 must be reported to sponsor within 10 days 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.
- **Possibly 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.
- **Probably 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.

The investigator will assess intensity for each AE and SAE reported during the investigation and assign it to one of the following categories:

- **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.

20.8 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 and ethics committees, as applicable.

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).

20.9 Medical Advisor Safety Review

The Sponsor is responsible for ensuring all Serious Adverse Event (s) are provided to the Medical Advisor for review and discussion.

The Medical Advisor will be informed of the following:

- All serious adverse events related to the investigation product or clinical investigation and serious adverse device effects
- 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
- New findings and/or updates in relation to already reported serious events

In addition, the Medical Advisor will receive lists of any reported AE's and ADE's related to the investigation product or clinical investigation, as defined by sponsor for a review of safety.

Correspondence, decisions, and recommendations regarding safety in the Clinical Investigation from the Medical Advisor must be documented and saved electronically in the Sponsor File.

20.10 Data Safety and Monitoring Board (DSMB)

The review of all safety data will be conducted on an ongoing basis to identify any potential safety issues. If needed, the Medical Advisor can call for a Data Safety and Monitoring Board meeting with relevant members, to discuss potential safety issues and further recommendations, if relevant.

Based on the safety data review, the Medical Advisor along with the DSMB may recommend that the sponsor modifies, temporarily suspends, or terminates the clinical investigation.

Correspondence, decisions, and recommendations regarding safety in the Clinical Investigation from the Data Safety and Monitoring Board must be documented in meeting minutes and saved electronically in the Sponsor File.

All final decisions, however, regarding clinical investigation modifications, remain with the Sponsor.

21 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 IRB. If monitoring or auditing of the clinical investigation identifies serious or repeated deviations, sponsor will suspend or terminate the particular investigation site. The sponsor or investigator will inform the IRB about the termination of the site.

If suspension or termination of the clinical investigation occurs, the investigator(s) will promptly inform the enrolled subjects. Sponsor will provide resources to fulfil the obligations from the CIP for follow-up of the subjects, as necessary.

22 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 IRB.

23 Publication policy

The results of the investigation, positive as well as negative, may be communicated by abstracts, posters, or oral presentations provided that opportunity is given for sponsor to discuss the contents and any conclusions drawn, before the abstract, paper, or visual presentations are finalised. In all cases the subject's identity will remain confidential.

Sponsor will undertake to comment on the draft documents within 30 working days of receipt, but the final decision on the contents and format of the publication from the conclusions drawn, will remain with the authors.

No preliminary results will be published (if sub studies are performed using an umbrella CIP, results and conclusions for each sub investigation can be published).

Data from the investigation is considered confidential until it is published according to the conditions of this CIP.

Sponsor may publish single subject case stories at any time during and after the investigation.

Sponsor reserves the right to use the data (published and unpublished) for reimbursement or regulatory purposes.

24 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.

25 References

1. Grossfeld GD, Litwin MS, Wolf JS, et al. Evaluation of asymptomatic microscopic hematuria in adults: the American Urological Association best practice policy--part I: definition, detection, prevalence, and etiology. *Urology.* 2001;57(4):599-603.

2. Grocela JA, Jura YH. Top-Vented Urinary Drainage Catheters Cause Fewer Epithelial and Vascular Changes in the Bladder Mucosa Compared to Conventional Catheters and May Reduce Susceptibility to Urinary Tract Infections. *Current Urology.* 2010;4(3):136-141.