Clinical Investigation Plan

CP290

Explorative clinical study investigating the performance and acceptance of new intermittent catheters in healthy volunteers

August 2018– January 2019

Master

NCT04231149

Document date: 10/18/2022

CHANGE LOG

VERSION NUMBER	ISSUED BY *(INITIALS)*	COMMENTS (MAJOR CHANGES SINCE LAST REVISION)
1.0	[redacted]	Document established in template version 5.0
2.0	[redacted]	Description of test product 1, 2 and 3 has been updated in section 2.0 (Identification and description of the investigational device) and 2.1.4 (description of investigational device). Section 6.1.1 (End points and rationale for selection) has been updated. Section 6.4.4 (Flowchart) has been updated due to changes in end points.
3.0	[redacted]	Follow-up procedure for terminated subjects added in section 6.3 Bladderscanner has been added in section 6.4.1 and 6.6 Timelines has been changed from Jun-sep 2018 to Aug to Dec 2018 Description of subject consent to tape record and film during interview have been added in section 6.1, 6.4.1 and 13.
4.0	[redacted]	Testproduct 1 has been withdrawn from the clinical investigation due to medical issues. Therefore visit 4 has been removed. Clarification of analysis/model split in part A and B. New Clinical Manager Medical advisor removed as this is handled by PI Timelines changed from August – December 2018 to August 2018- January 2019

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> SYNOPSIS OF THE CLINICAL INVESTIGATION

Objective

The primary objective of the investigation is to obtain indications that the intermittent catheters [redacted] can be used to void and empty the bladder

Primary end point and secondary end point(s)

The primary endpoint is: Urine flow rate

The secondary endpoints are: Post void residual urine, haematuria (macroscopic and microscopic) and adverse events.

Explorative endpoints are: Overall discomfort during catheterisation, discomfort during insertion, discomfort during withdrawal, discomfort during urination post catheterisation and handling during catheterisation.

Pass/fail criteria

No formal success criteria are applied in this explorative investigation. The investigation will provide valuable insight into both performance and acceptance of three new intermittent catheters [redacted]

Design of the investigation

The study is a single blinded, randomised, cross-over study [redacted].

- **Part A** evaluates two prototypes of intermittent catheters compared to the standard catheter SpeediCath® Flex in randomised order (Test visit 1-3)
[redacted]

In the investigation ten healthy males will be included. The subjects will be catheterised once per visit. During the test visits the primary, secondary and explorative endpoints will be registered. The visits will be conducted at Coloplast A/S, Holtedam 1-3, 3050 Humlebæk.

Subjects will be asked to participate in an interview in continuation of their last visit for part A (Test Visit 3[redacted] The interviews will be performed by a Coloplast representative asking questions related to their experience with the catheter. In addition, a Coloplast representative will interview the Investigator and her representatives after LPO with questions related to their experience with the catheters.

The investigation is planned to be conducted in August 2018-January 2019. The visit window will be minimum five days between the visits (catheterisations), to ensure time for healing of any potential urethral trauma. [redacted]. However, the maximum time between visits should be adjusted to ensure the subject is terminated before LPO.

Population

Inclusion criteria	Exclusion criteria
Has given written informed consent and signed letter of authority	Has a previous history of genitourinary disease including congenital abnormalities and surgical procedures performed in the urinary tract
Is at least 18 years of age and has full legal capacity	Has symptoms of urinary tract infections (frequent urination, stinging and pain at urination)
Is a male	Are participating in any other clinical investigation related to urinary tract system during this investigation (inclusion to termination)

Willing to comply without using analgetica[1] up to 24 hours prior to catheterisation visits	Known hypersensitivity toward any of the test products
Has a negative urine multistix for erythrocytes (microscopic haematuria), leukocytes and nitrite	Haematuria is an explorative end point. If subjects have haematuria when entering the investigation, it could affect the evaluation of data. Haematuria could also be a sign of Urine Tract Infections (UTI) which is also an exclusion criterion

Test products

The investigational devices are intermittent catheters for single use only and are intended to be used for drainage of the bladder through the urethra. The test products will be similar to the CE marked SpeediCath® Flex catheter (comparator) with a few exemptions in the raw catheter, see section 2.1.4. [redacted]

Investigation approval

The investigation will be approved by the Ethical Committee in Denmark and the Danish Medicines Agency before investigation initiation.

1. List of personnel involved in the Investigation

1.1. Sponsor representatives

COORDINATING CLINICAL MANAGER	STATISTICIAN
[redacted]	[redacted]
MEDICAL AFFAIRS PROJECT MANAGER	**DATA MANAGER**
[redacted]	[redacted]
SCIENTIFIC MANAGER	
[redacted]	

In case of emergency, please contact the Clinical Manager.

1.2. Investigators

The Clinical manager is responsible for maintaining an updated list of all PIs, investigation sites and institutions.

SITE 1 – DK001 - PRINCIPAL INVESTIGATOR
[redacted]

1.3. Other

All delegated tasks from Investigator to Study Nurses will be documented in the Site Personnel Signature and Delegation List.

2. Identification and description of the investigational device

The investigational devices are intermittent catheters for single use only and are intended to be used for drainage of the bladder through the urethra. The investigational catheter devices are similar to the CE marked SpeediCath® Flex, with a few exemptions in the raw catheter, see section 2.1.4. [redacted]

2.1. Manufacture

The investigational device [redacted] will be manufactured by:

Coloplast A/S
Holtedam 1
3050 Humlebæk
Denmark

2.1.1. Identification, traceability and labelling of device

The investigational catheter devices (Test product 2 and 3) [redacted] will be labeled as shown in figure 1. SpeediCath® Flex used in CP290 is already CE marked and is labelled accordingly. The investigation will only be conducted in Denmark, therefore the labels are only printed in Danish.

Figure 1: Labelling for the investigational catheter devices (Test product 2 and 3) [redacted]

***Will be adjusted according to the type of test product. ** Will be adjusted according to the lot.**

2.1.2. Clinical investigation purpose of device

The investigation test devices (Test product 2 and 3) are intended for transient (less than 60 minutes) intermittent drainage of the bladder. [redacted].

The test devices are indicated for drainage from the bladder through the urethra in healthy male volunteers. There are no proposed contraindications.

2.1.3. Intended population for the device

The intended population for the devices are healthy male volunteers.

2.1.4. Description of investigational device

Intermittent Catheters (Figure 2)

The investigational catheter devices are for single use only and are intended to be used for drainage of the bladder through the urethra. The products are intended to be used by healthcare professionals on healthy volunteers in the clinical investigation CP290.

[redacted].

The investigational catheter tubes will be similar to the CE marked SpeediCath® Flex with a few exemptions in the raw catheter. [redacted]

The remaining parts of the investigational catheter devices are identical. All materials used for the investigational catheter devices are identical to the already CE marked SpeediCath® Flex.

The investigational catheters (Test Product 2 and 3) and Comparator (SpeediCath® Flex) are classified as class I sterile device [redacted] according to the Medical Device Directive, MDD 93/42/EEC, Rule 5. [redacted]

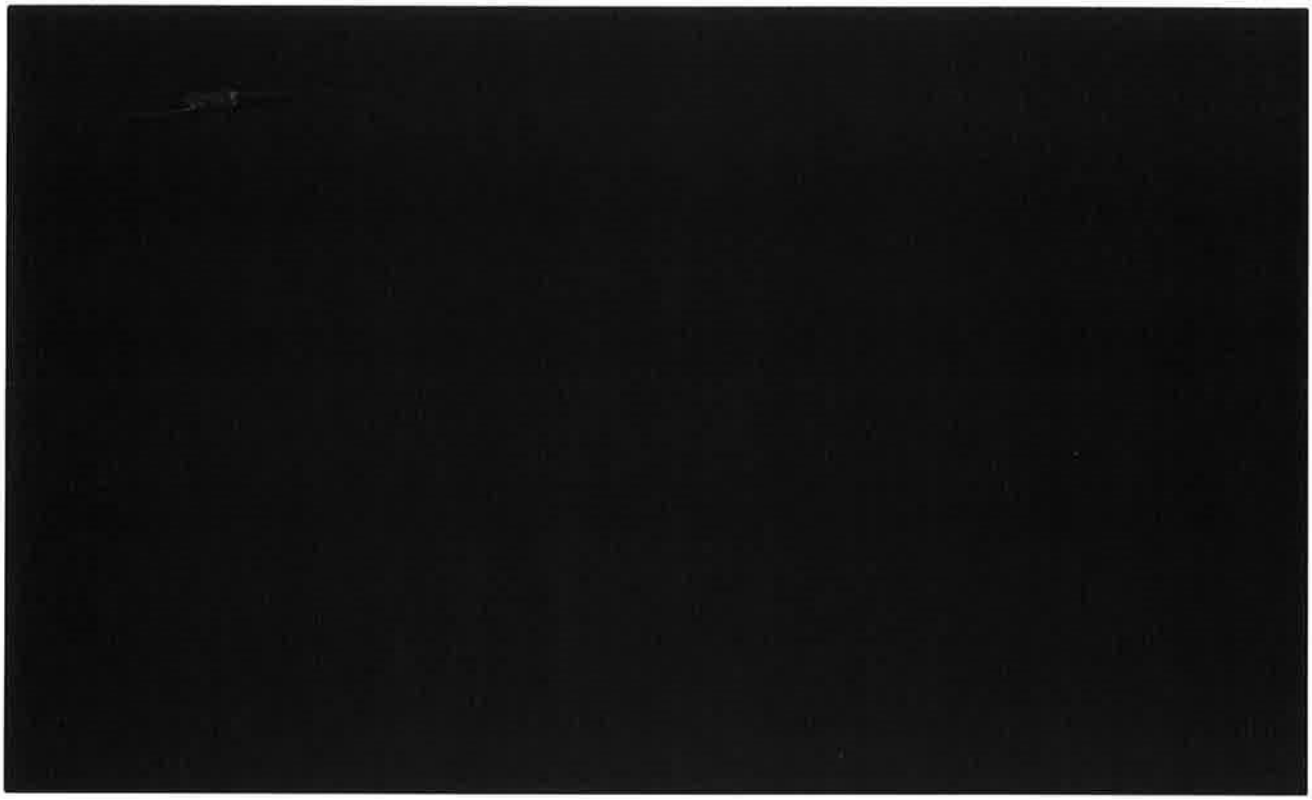


Figure 2: Illustration of SpeediCath® Flex and Test products 2 and 3 (raw catheters).

2.1.5. Handling and training

The handling of the test products [redacted]. The test products are to be handled in the same way as the comparator which the study nurse is experienced in using.

The investigational device (catheters) are for single use. The IFU consists the warning: "Reuse of this single use product may create a potential risk to the user. Reprocessing, cleaning, disinfection and sterilisation may compromise product characteristics which in turn create an additional risk of physical harm to or infection of the user".

Products should be stored at room temperature and away from direct sunlight, which described in the labelling.

[redacted]

For further details, please see the Investigators Brochure.

2.1.6. Comparator product

The CE-marked Standard SpeediCath® Flex (Nelaton, CH12) will be used as comparator in this investigation. As the comparator product is already on the market and will be used within the intended use in this clinical investigation, it is not considered an investigational device per ISO 14155:2011 and is thus not described here. Please refer to the ISO 14155:2011 for details.

3. Justification for the conduct of the clinical investigation

Intermittent catheterisation is the preferred method of bladder emptying for persons with spinal cord injuries and neurogenic bladder dysfunction. Coloplast A/S manufactures different catheters for intermittent catheterisation and works continuously to improve them.

The newly developed prototypes have not previously been evaluated in the human urethra and a clinical investigation is required to demonstrate performance and acceptance.

4. Investigational device and clinical investigation risks and benefits

The clinical investigation is conducted in accordance with current law and applicable standards, see section 12. The rights, safety and well-being of human subjects shall prevail over interest of science of society.

The clinical investigation is conducted in accordance with "The Declaration of Helsinki, 1964, last amended at the 64th WMA General Assembly, Brazil, October 2013".

4.1. Anticipated benefits

By participating in this investigation, the subjects will contribute with important information for developing new intermittent catheters [redacted], that in turn may benefit individuals who are dependent on catheters for emptying their bladder.

4.2. Anticipated risks, side effects and disadvantages

Risks associated with the investigation may be discomfort or stinging in the urethra during the catheterisation. Furthermore, there may be a risk of micro trauma and haematuria after catheterisation, which heals within 1-3 days. The test catheter is not expected to produce more stinging or discomfort compared to any other standard catheter on the market.

Possible interactions with concomitant medical treatments

There is no known interaction between the use of catheters and concomitant medication. However, the use of analgesics must be avoided up to 24 hours prior to catheterisation visits during this investigation, since pain relief could affect primary an explorative endpoints and general experience of catheterisation.

Steps that will be taken to control or mitigate the risks

All subjects are encouraged to contact the investigator in case of problems or unwanted side effects. During the investigation, all subjects will be enquired about their health and eventual problems (including issues mentioned here) by the investigator or representative at every visit. In addition, trained health professionals will perform the catheterisations.

Risk-to-benefit rationale

The risk and disadvantage of participating in the investigation are estimated to be low. The healthy volunteers will not have any benefits from this investigation, but catheter users may in the future benefit from a new and improved catheter and methods for faster voiding.

5. Objectives and hypotheses of the clinical investigation

5.1. Objective

The primary objective of the investigation is to obtain indications that the intermittent catheters [redacted] can be used to void and empty the bladder.

5.2. Hypotheses

It is hypothesised that the catheters with the new design increase urine flow rate and/or reduce post void residual urine compared with the CE-marked SpeediCath® Flex without worsening overall discomfort during catheterisation.

6. Design of the clinical investigation

Table 1: Overview of the design of the investigation. The investigation is single blinded, cross-over, randomised divided into two parts; Part A and Part B.

Visit		Days to next visit
Information visit	Oral and written information about the investigation	
Inclusion visit (V0)	Inclusion	
Part A		
Test Visit 1 (V1)	Catheterisation with randomised product 1	≥ five days
Test Visit 2 (V2)	Catheterisation with randomised product 2	≥ five days
Test Visit 3 (V3)	Catheterisation with randomised product 3	≥ five days
[redacted]		

6.1. General

This study is a single blinded, randomised, crossover study divided into two parts; Part A and Part B. The study period consists of an information visit, an inclusion visit, six test visits and a termination visit.

- **Part A** evaluates two prototypes of intermittent catheters (Test product 2 and 3) compared to the standard catheter SpeediCath® Flex (Comparator).

[redacted]

In the investigation ten subjects will be included. The subjects will be catheterised once per visit. In part A (Test Visit 1-3) the subjects will be catheterised with the two test catheters and comparator in a randomised order. [redacted]. The order of the catheterisations will be randomised to prevent bias.

During the test visits the primary, secondary and explorative endpoints will be registered.

Subjects will be asked to participate in an interview in continuation of their last visit for part A (Test Visit 3) [redacted]. The interviews will be performed by a Coloplast representative asking questions related to their experience with the catheter. The subjects must sign a separate consent form for this purpose and can participate in the investigation without participating in the interview. In addition, subjects will be asked for consent to tape recording and filming during the interviews, but can participate in interviews without this.

In addition, a Coloplast representative will interview the Investigator and her representatives after LPO with questions related to their experience with the catheters.

The investigation is planned to be conducted in August 2018-Januar 2019. The visit window will be minimum five days between the visits (catheterisations), to ensure time for healing of any potential urethral trauma. [redacted] However, the maximum time between visits should be adjusted to ensure the subject is terminated before LPO.

No biobank will be established for this investigation. All urine samples in the clinical investigation (for evaluating in- and exclusion criteria and for evaluating end points) will be destructed immediately after analysis.

6.1.1. End points and rationale for selection

	End points	Type of assessment	Rationale for selection of end points
Primary end points	Urine flow rate	- Max flow ($\frac{ml}{s}$) - Middle flow ($\frac{ml}{s}$)	Urine flow rate, measured by uroflowmetry, are an indicator for the test product performance. [redacted]
Secondary end points	Post void residual urine	Amount of urine left in bladder (ml)	Post void residual urine, measured with an ultrasound bladder scan are indicator for the test product performance.
	Haematuria – macroscopic	Did you experience visual blood during catheterisation (No/Yes) If yes, where was the blood (several answers accepted) (On the tip – at the eyelets – on the whole catheter – in the urine)	Macroscopic haematuria is measured by assessing visible blood during catheterisation. This is an indicator for test product safety.
	Haematuria - microscopic	7 answer possibilities Negative - Neg - Non-hemolysed 10 Ery/µL (+/-) - Hemolysed 10 Ery/µL (+/-) Positive - Non-hemolysed 80 Ery/µL (2+) - Hemolysed 25 Ery/µL (1+) - Hemolysed 80 Ery/µL (2+) - Hemolysed 200 Ery/µL (3+) At least one positive response makes endpoint considered posi-tive	Microscopic haematuria will be measured after each catheterisation using urine dipstick. This is an indicator for test product safety.
	Adverse events	Adverse event form	This is an indicator for test product safety.
Explorative end points	Overall discomfort during catheterisation	On a scale ranging from "no discomfort" to "worst possible discomfort" caused by the catheter, set a	Discomfort will be measured both during catheterisation, insertion, withdrawal and during urination post catheterisation

	End points	Type of assessment	Rationale for selection of end points
		vertical line indicating how you experienced the overall catheterisation.	to investigate potential differences. Discomfort is measured by VAS-scale (10 cm horizontally line) – (assessed by subjects)
	Discomfort during insertion	On a scale ranging from "no discomfort" to "worst possible discomfort" caused by the catheter, set a vertical line indicating how you experienced the insertion of the catheter.	
	Discomfort during withdrawal	On a scale ranging from "no discomfort" to "worst possible discomfort" caused by the catheter, set a vertical line indicating how you experienced the withdrawal of the catheter.	
	Discomfort during urination post catheterisation	On a scale ranging from "no discomfort" to "worst possible discomfort" caused by the catheter, set a vertical line indicating how you experienced urination after the catheterisation.	
	Handling during insertion	How did you experience insertion of the catheter? (5 point scale: Very difficult – difficult – neither difficult nor easy – easy – very easy)	As the catheter design is relatively new, handling will be investigated and the information utilized in further development.
	Handling during withdrawal	How did you experience withdrawal of the catheter? (5 point scale: Very difficult – difficult – neither difficult nor easy – easy – very easy)	
	Handling during insertion	Did you touch the coated part of the catheter during insertion? (Yes/No)	
	Handling during catheterisation	Did you experience urine running out of the catheters on the outside of the catheters? (Yes/No)	
	Urine flow	- Micturition time (sec) - Flow time (sec) - Time to Qmax (sec) - Micturition volume (ml)	Urine flow, measured by uroflowmetry, are an indicator for the test product performance. [redacted]

6.1.2. Discussion of clinical investigation design

This study is a single blinded, randomised, crossover study divided into two parts, with healthy subjects.

A cross-over design has been chosen over a parallel design due to minimisation of interpersonal variation. Only blinding of subjects is possible, since nurses will catheterise and since there is a visual difference in the products. A lower number of subjects are required with this study design as each subject act as his own control.

Healthy subjects have been chosen since discomfort must be evaluated by subjects with normal urethral sensation. As this is an exploratory study no formal sample size calculation has been performed. However, it is assumed that ten subjects will be adequate for obtaining indications on performance and acceptance.

During the investigation, there must be a minimum of five days between each visit/catheterisation to allow potential micro trauma from the catheterisations to heal.

6.2. Investigational device and comparator(s)

During the study period, each subject will be exposed to one catheterisation per Test product 3, and [redacted] per Test product 2 and comparator. A total amount of ten of each test products and 20 comparator products are needed in the study. However, to ensure that the site has enough, more products than needed will be provided by Sponsor to the site. All products will be accounted for.

Each catheterisation lasts approximately 15 minutes totally.

Table 2: Overview of products needed in the investigation

Product	Description	Number of catheters needed/subject	Number of catheters needed in total
Test product 2	Prototype 2 of intermittent catheter	1	10
Test Product 3	Prototype 3 of intermittent catheter	1	10
Comparator	SpeediCath® Flex	1	10
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Supplementing devices [redacted] instruments normally used for catheterisation (e.g. medical gloves, tray for urine collection) are supplied by Sponsor. Urine bags should not be connected to the catheters as this may affect the handling of the product. Neither may catheter accessories as gels be used on the catheter as this may affect the data.

6.3. Subjects

To be included in the investigation, the subjects must comply with the selection criteria described in section 0 and 6.3.2.

Subjects that has terminated the study will be informed to contact investigator in case of any questions during the study, and their general practitioner in case of any questions later than one week of investigation termination.

6.3.1. Inclusion criteria for subject selection

Subjects interested in participating the clinical investigation must comply with the following criteria:

Inclusion criteria	Justification for inclusion criteria
Has given written informed consent and signed letter of authority	To ensure voluntarily and that Helsinki Declaration is met. Letter of Authority is a demand from Danish Medicines and Health Authorities
Is at least 18 years of age and has full legal capacity	To meet Helsinki Declaration
Is a male	Males are considered 'worst case' since their urethra is longer
Willing to comply without using analgetica[2] up to 24 hours prior to catheterisation visits	Pain relief could affect primary and explorative endpoints and general experience of catheterisation. The 24 hours are chosen based on use of most common analgesics (Ibuprofen, paracetamol and aperin) which have a half-life (T½) of two hours. Using safety equation of T½ x five hours gives ten hours, where 3% is left in the body. The 24 hours is given as safety margin and is more practical in the investigation
Has a negative urine multistix for erythrocytes (microscopic haematuria) Definition of negative/positive results for Multistix erythrocytes: Negative: Negative. Non-haemolysed 10 Ery/µL (+/-) Haemolysed 10 Ery/µL (+/-) Positive: Non-haemolysed 80 Ery/µL (2+) Haemolysed: 25 Ery/µL (1+) 80Ery/µL (2+) 200 Ery/µL (3+)	Haematuria is an explorative end point. If subjects have haematuria when entering the investigation, it could affect the evaluation of data. Haematuria could also be a sign of Urine Tract Infections (UTI) which is also an exclusion criterion
Has a negative urine multistix for leukocytes Definition of negative/positive results for Multistix Leukocytes: Negative: Negative Positive: 15 (1+)	To ensure that subject does not have UTI at inclusion

[2] Medicines for systemic usel hat are pain relieving without significantly affecting the consciousness

70 (2+) 125 (3+) 500 (4+)	
Has a negative urine multistix for nitrite	To ensure that subject does not have UTI at inclusion

6.3.2. Exclusion criteria for subject selection

Subjects complying with the following criteria must be excluded from participation in the clinical investigation:

Exclusion criteria	Justification for exclusion criteria
Has a previous history of genitourinary disease including congenital abnormalities and surgical procedures performed in the urinary tract	To ensure homogeneous group of urinary tracts where abnormalities, diseases or surgical procedures do not influence on the subjects perception of the catheters
Has symptoms of urinary tract infections (frequent urination, stinging and pain at urination)	To ensure that the subjects do not have UTI at inclusion. None of the symptoms may be present.
Are participating in any other clinical investigation related to urinary tract system during this investigation (inclusion to termination)	To eliminate uncertainly whether any Adverse Events (AE's) or Serious Adverse Events (SAE's) occurring during the study to relate to use of the herein tested products, and to eliminate unintentional affect from other devices/medicines on the study's data
Known hypersensitivity toward any of the test products	Asked by competent authorities

6.3.3. Recruitment and enrolment

Recruitment of potential subjects will begin once approvals have been obtained from the Danish Medicines Agency and the Ethics Committee. The recruitment process for this investigation is described in Table 3.

Table 3: Overview of the recruitment process

Recruitment method	www.forsøgsperson.dk	Advertisement
Potential subjects	Subjects will be recruited through www.forsøgsperson.dk where potential subjects can gather information on clinical investigations. The contact information for Clinical manager or a representative hereof will be available at the site.	Advertisement i.e. in local shops, sports facilities, local newspapers and social media. The advertisement will state the contact information for Clinical Manager or a representative hereof.
First contact	Interested potential subjects contact Clinical Manager at Coloplast A/S or a representative hereof.	
Second contact	The Clinical Manager, a representative hereof or the study personnel will contact interested potential subjects by phone and give a short introduction to the investigation.	
Subject Information Form	If a potential subject is still interested in participating, then written information about the investigation (subject information form) will be sent to the subject to ensure that potential subjects are given the opportunity to read about the investigation before a possible informational visit, and so that they can prepare any possible questions they may have. The subject information provides information to potential 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.	

	In addition, the potential subjects will receive an additional letter about subjects rights in Denmark: "Forsøgspersoners rettigheder i et sundhedsvidenskabeligt forskningsprojekt".
First visit Information visit	If a potential subject is interested in participating after reading the subject information form, a visit (visit 0) will be arranged in a room reserved to ensure privacy and quiet surroundings at the investigators clinic/department. When arranging the visit, it will be ensured, that the subject has received the Information Form prior to the visit. The subjects will receive both written and verbal information about the possibility of bringing a companion to the informational visit and to any possible subsequent visits. See section 13 for information to be given to the subjects, as well as the informed consent process.

6.3.4. 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. 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:

- Non compliance with the CIP impacting the scientific integrity of the investigation.
- If subject's safety and wellbeing is compromised by further participation.

A subject who is withdrawn from the investigation, for any reason, will be encouraged to contact the investigator if problems arise that the subject believes are related to the clinical investigation. Subjects who have not experienced any adverse events will not be followed up. For subjects who experience adverse events, see section 14.

6.3.5. Point of enrolment

A subject is considered enrolled in the investigation when the written informed consent is obtained. The expected duration for each subject is described in section 6.1.

6.3.6. 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. Changes greater than ± 3 months will be notified to EC and regulatory authorities.

- Submission to Ethics Committee and Competent Authorities (Mid March 2018)
- First subject enrolled (AUG/2018).
- Last subject enrolled (NOV/2018).
- Last subject completed (JAN/2019).
- Data Presentation (FEB/2019)
- Final report (DEC/2019).

6.3.7. Total number of subjects

As this is an exploratory investigation no formal sample size calculation has been performed. It is assumed that ten subjects will be adequate for obtaining indications on performance and acceptance.

6.4. Procedures

6.4.1. Clinical investigation-related procedures

Before initiation of the clinical investigation, sponsor must be provided with key personnel's signed and dated curriculum vitae (not more than two 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.

The investigation consists of an inclusion visit and five test visits. For an overview see flow-chart in section 6.4.4.

Inclusion visit (V0) – approx. one hour
Information:
If a potential subject is interested in participating after the short oral introduction by phone and reading the subjects information form, an information visit will be arranged in a room reserved to ensure privacy and quiet surroundings at the site. When arranging the visit, it will be ensured, that the subject has received the Subject Information Form prior to the visit. The subjects will receive both written and verbal information about the possibility of bringing a companion to the informational visit and to any possible subsequent visits. During the information visit the Investigator or delegated personnel will provide oral information about the investigation based on the Subject Information Form. The subjects have the right to wait 24h before deciding on participation. The information visit and the Visit 0 can be the same day.

Informed consent:
If/when the subject decides to participate he will be asked to sign the Informed Consent Signature Form and other relevant forms (see section 13). If a subject so desires, and it is certain that it is understood what the investigation entails and the relevant forms have been signed, it is then ensured that in- and exclusion criteria are met, including urine analysis (leukocytes, nitrite and erythrocytes). Enrolled subjects are allocated a subject number, randomisation is performed and hereafter demographics, baseline data and concomitant medications is recorded by Investigator or delegated personnel.
Visit 0 and Test Visit 1 can be combined.

Test Visit (V1-V3) – approximately two hours
Subject is asked about symptoms for urinary tract infections (frequent urination, stinging or pain at urination) and use of analgetica up to 24 hours prior to the visit. In addition, a urine sample is made and microscopic haematuria, nitrite and leukocytes is measured before catheterisation to further ensure no symptoms of urinary tract infection or damage to the urinary tract system. If negative for these symptoms, use of analgetica and microscopic haematuria/nitrite/leukocytes, the subject will be catheterised with the randomised product and urine flow rate is measured. Hereafter the bladder is scanned for post void residual urine, by using a hand held bladderscanner, [redacted]. The subject is offered something to drink and after 1-2 hours a urine sample is made and microscopic haematuria measured. Subject and nurse register relevant answers in CRF, including possible adverse events. In addition, subject register the end points regarding discomfort (VAS-scale) and the nurse register the assessments in the CRF. Next visit is scheduled.
If subjects have agreed to participate in interviews, Test Visit 3 will be prolonged to include interview.

Test Visit (V5-V6) – approximately two hours
Subject is asked about symptoms for urinary tract infections (frequent urination, stinging or pain at urination) and use of analgetica up to 24 hours prior to the visit. In addition, a urine sample is made and microscopic haematuria, nitrite and leukocytes is measured before catheterisation to further ensure no symptoms of urinary

tract infection or damage to the urinary tract system. If negative for these symptoms, use of analgetica and microscopic haematuria/leukocytes/nitrite, the subject will be catheterised with the randomised product [redacted] and urine flow rate is measured. Hereafter the bladder is scanned for post void residual urine, by using a hand held bladderscanner, [redacted]. The subject is offered something to drink and after 1-2 hours a urine sample is made and microscopic haematuria measured. Subject and nurse register relevant answers in CRF, including possible adverse events. In addition, subject register the end points regarding discomfort (VAS-scale) and the nurse register the assessments in the CRF. Next visit is scheduled.
If subjects have agreed to participate in interviews, Test Visit 6 will be prolonged to include interview. At the end of Test Visit 6 the termination page in CRF is completed by nurse.

Interview – plus one hour
Subjects will be asked if they would like to participate in interviews following Test Visit 3 and 6. A Coloplast representative will interview the subjects asking questions related to their experience with the catheter. The subjects will be asked to sign a specific consent form to participate in interview. In addition, subjects will be asked for consent to tape recording and filming during the interviews, but can participate in interviews without this. The investigator and/or study personnel will be interviewed by a Coloplast representative asking questions related to their experience with the catheters.

Urinary tract infection suspicion
If the subject shows symptoms of urinary tract infections he will be referred to his own physician for further examination. When the subject has been examined and treated for eventual urinary tract infections, and shows no symptoms for urinary tract infections, his visits can be rescheduled if possible before LPO. If not possible to complete all visits before LPO, the subjects should complete all possible visits.

Use of analgesics
If the subject used analgesics within 24 hours prior to a visit, this will be documented in the Concomitant Medication Form and the visit will be rescheduled.

6.4.2. Activities performed by sponsor representatives

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

- Training of investigator and study personnel in the informed consent procedure, study procedures, how to use the products, complete the CRF, how to report possible safety issues and in ISO 14 155. All training will be documented by site
- Support during the recruitment process and conduct of the investigation
- Monitoring
- Perform the interviews

6.4.3. Foreseeable factors that may compromise the outcome / results

No foreseeable factors are expected to compromise the outcome/results of the design.

6.4.4. Flow-chart

Table 4 chart showing the connection between visits and assessments.

General	PERFORMED BY	SOURCE	INFORMATION AND INCLUSION VISIT 0	VISIT 1-3	VISIT 5-6	TERMINATION VISIT
Oral information	Investigator	NA	X			
Written informed consent	Subject	Informed consent form	X			
Signed Letter of authority	Investigator	Letter of Authority Form	X			
Consent to interview	Subject	Informed consent form - Interview	X			
Check of in- and exclusion criteria	Investigator	CRF	X			
Allocation to subject number	Investigator	CRF	X			
Randomisation	Investigator	Randomisation Envelope	X			
Insurance of subjects well-being and compliance with CIP	Investigator	CRF	X	X	X	X
Registration of Demographic						
Date of birth	Investigator	CRF	X			
Check for symptoms of UTI, damage to urine tract system and use of analgesics before catheterisation						
Urine sample from subject	Subject	NA		X	X	
Leukocytes (urine dipstick)	Investigator	CRF		X	X	
Nitrite (urine dipstick)	Investigator	CRF		X	X	
Haematuria – microscopic (urine dipstick - erythrocytes)	Investigator	CRF		X	X	
Check for use of analgesics 24 hours before catheterisation	Investigator	CRF		X	X	
Catheterisation per randomisation	Investigator	CRF		X	X	
Registration/measurement of primary end points – during catheterisation						
Urine flow rate - Max flow ($\frac{ml}{s}$) - Middle flow ($\frac{ml}{s}$)	Investigator	CRF (or possible printed graph)		X	X	
Registration/measurement of secondary end points - after catheterisation						
Post void residual urine	Investigator	CRF (or possible print)		X	X	
Haematuria – macroscopic (visible blood)	Investigator	CRF		X	X	
Urine sample from subject	Subject	NA		X	X	
Haematuria – microscopic (urine dipstick)	Investigator	CRF		X	X	
AEs/ADEs/SAEs/SADEs	Investigator	CRF		X	X	X
Registration of explorative end points						
Overall discomfort during catheterisation	Subject	CRF		X	X	X
Discomfort during insertion	Subject	CRF		X	X	

Discomfort during withdrawal	Subject	CRF		X	X	
Discomfort during urination post catheterisation	Subject	CRF		X	X	
Handling during insertion	Investigator	CRF		X	X	
Handling during withdrawal	Investigator	CRF		X	X	
Handling during insertion	Investigator	CRF		X	X	
Handling during catheterisation	Investigator	CRF		X	X	
Interview	Coloplast representative	Interview notes		V3	V6	
Urine flow - Micturition time (sec) - Flow time (sec) [redacted] - Micturition volume (ml)	Investigator	CRF (or possible printed graph)		X	X	
Registration of termination						
Termination form. Completed	Investigator	CRF				X

Investigator can delegate tasks to trained study personnel. This will be documented by the Delegation Log and Training Log.

6.4.5. Randomisation Procedure

At the inclusion visit each subject will be allocated randomly into to one of the possible catheterisations orders for the first four catheterisations and then again into one of two possible catheterisation orders for the last two catheterisations. Subjects are allocated to a randomisation number per a randomisation list generated automatically by computer (SAS). The investigator or a representative hereof opens a sealed, non-transparent envelope with the randomisation block inside. Randomisation number is registered in the CRF by investigator or a representative. The randomisation list is archived in Sponsor File.

6.4.6. Blinding

During the investigation, the subject will be blinded with a curtain so he will not be able to see which catheter is used. The nurse is not blinded as it is not possible to blind the products due to visible differences. It is a disadvantage that it is not possible to blind the nurses as there could be some bias in their assessment of the products tested. However, it is the subject who assesses the secondary end points regarding discomfort (VAS) during catheterisation and micturition.

6.4.7. Case Report Forms

All assessments and observations throughout the investigation for each subject must be carefully recorded in the CRF. The CRFs are printed and supplied by Sponsor. A CRF is provided for each subject. It is the responsibility of the Investigator that all data are entered promptly and correctly. Each CRF have printed instructions for completion.

The CRF for each subject will be divided in two parts; one for the investigator or representative to complete (Investigator Binder) and one for the subjects two complete (Subject Binder). The study personnel will be responsible for guiding the subject on how to complete the subject's part of the CRF. The CRF will clearly state which parts are to be completed by whom. The subject's part will be the pages regarding discomfort during insertion and withdrawal of the catheter measured by the VAS-scale. These pages will be in Danish. After

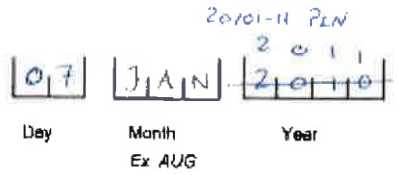
completion by subject, the study nurse or investigator will measure the VAS-scale and write the measurement in the CRF.

The sponsor will be responsible for training the investigator and the investigation personnel in completion of the CRF. Only personnel who have signed the Site Personnel Signature and Delegation Log and the Clinical Investigation Training Log will fill in the Investigator Binder.

It will be the responsibility of investigator that all measurements and observations are correctly noted with a pen (permanent writing utensil) in the CRF.

Any correction in the CRF must be clearly signed and dated by authorised site personnel. The entry corrected must be crossed out so that the entry is still legible.

Example 1:



Example 2:

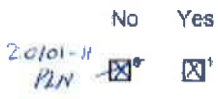


Figure 4 Two examples of how to make corrections in the CRF

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

The completed CRFs will be collected ongoing after monitoring.

6.5. Concomitant treatment

Healthy subjects may not use analgesics 24 hours prior to catheterisation visits, see inclusion criteria. Subjects may not participate in other clinical investigations related to urinary tract system during this investigation.

6.6. Supplementary materials and equipment

Supplementing devices or instruments normally used for catheterisation (e.g. medical gloves, tray for urine collection), the uroflow meter and equipment for ultrasound measurements are supplied by Sponsor.
The intermittent catheters [redacted] used in the investigation will be supplied by Sponsor.
For bladder scanning, a hand held [redacted] will be used. The bladder scanner will be supplied by Sponsor.

6.7. Monitoring Plan

During the period of the investigation monitoring is planned and carried out by the Clinical Manager.

Before doing any review of subject data, the Clinical Manager must review the signed Informed Consent Form(s) and only monitor data from subjects with a correct signed Informed Consent Form.

The first monitoring visit (Mon 1) at the site should be conducted as soon as reasonably possible after the first subject at the site has completed the first visit of the investigation to minimise systematic errors done by site.

Additional monitoring will be conducted in accordance to the recruitment rate:

- Monitoring visit two (Mon 2) will be conducted as soon as possible after the first five subjects have completed Part A.
- Monitoring visit three (Mon 3) will be conducted as soon as possible after the first five subjects have completed the investigation.
- Monitoring visit four (Mon 4) will be completed as soon as possible after the last subject has completed the investigation
- Monitoring visit five, Close out visit, will be conducted as soon as possible after database lock

Written informed consent, in- and exclusion criteria and all Adverse events occurring in the investigation will be 100% verified for timely completion for all subjects enrolled in the investigation.
Investigation Site File shall be monitored for 100% completion per the Investigation File Requirement Checklist. Monitoring activities conducted by the clinical manager will be documented in the site visit report applicable to the conducted visit. A summary describing the observation(s) and actions required shall be provided as soon as reasonably possible to the investigator after the conducted monitoring visit. The sponsor representative will have close contact to the site in the recruitment period to ensure that any concerns, problems or recruitment challenges are solved with the site in a timely manner.

6.7.1. Source data verification

Investigation source data are: the CRFs, Informed Consent Forms, Letter of Authority, randomisations envelopes, interview notes, output from uroflowmetry and print.

All data collected can be directly entered in the CRF and in case site write source data in medical records or nurse notes this will be described in the site specific "Source data specification form" (sponsor ref. number VV-0190745). Only the investigator, delegated site personnel and the sponsor representatives (personnel within Medical Affairs/Clinical Operations) will have access to all the CRFs.

6.7.2. Other methods for data quality assurance

The sponsor, sponsor's representative and/or investigational sites may be inspected by competent authorities or their representatives and likewise may be audited per Coloplast internal quality audit plan and procedures.

7. Statistical considerations

7.1. Statistical design, method and analytical procedures

Design
The study is a single blinded, randomised, crossover study divided into two parts; Part A and Part B.

- Part A evaluates 2 prototypes of intermittent catheters compared to a standard SpeediCath® Flex catheter.

[redacted]

Populations

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

The **ITT population** will be constituted by all randomised subjects with valid informed consent who have been exposed to at least one product, and with valid information on at least one product with respect to either primary or secondary endpoints. Any exclusion of subjects from the ITT set beyond this must be separately documented.

The **Safety population** (basis for AE summary) will be constituted by subjects that have given informed consent and have been exposed to at least one product.

A formal PP population is not planned due to the explorative nature of the investigation. Considering the data obtained it might however be considered to make additional explorative analyses 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 population. This could for example be due to protocol violations at one test day that would affect the primary endpoint at the corresponding test day, but have no impact on the primary endpoint on the remaining test days. Any exclusion of endpoints/data points will be documented.

General
All efficacy will be based upon the ITT (intention to treat) population and adverse events will be summarized based on the safety population.

If data is represented by a curve (e.g. pressure and force), relevant characteristics of the curve (e.g. peak of the curve) will be summarised and/or listed.

Where meaningful, data will be summarised and/or listed. Additional explorative post-hoc analyses can be performed if deemed relevant.

Primary endpoint
A mixed model, for part A and B respectively, with subject included as a random component will be applied for the primary analysis of the urine flow rate.

Treatment (SpeediCath® Flex, test product 2, test product 3 (part A) and SpeediCath® Flex catheter and Test product 2 (part B) [redacted]) and Day of catheterisation visit (1, 2, 3, 5 and 6) will be included as fixed effects with age as a covariate. The contrast between the catheters as well as the 95% confidence intervals will be estimated using Proc Mixed in SAS.

Secondary endpoints
Discomfort, measured on a VAS scale and post void residual urine will be analysed using a linear mixed model, for part A and B respectively, same as described in the primary endpoint

Adverse events will be summarised and/or listed based on the safety population.

Haematuria data will be listed.

The odds ratio between the test products as well as the corresponding 95% confidence intervals will be estimated.

All statistical analyses will be made with SAS version 9.4 (SAS Institute Inc., Cary, NC).

7.2. Sample size

As this is an exploratory study no formal sample size calculation has been performed. It is assumed that 10 subjects will be adequate for obtaining indications on performance and acceptance.

7.3. Level of significance and power

Statistical tests will be carried out as two sided tests on a 5% level of significance.

7.4. Drop-out

NA

7.5. Pass/fail criteria

No formal success criteria are applied in this explorative investigation. The investigation will provide valuable insight into both performance and acceptance of three new intermittent catheters [redacted]

7.6. Interim analysis

There is no planned interim analysis in this investigation.

7.7. Statistical reason for termination of investigation

There will be no interim analysis and therefore no reason to terminate the investigation based on statistical considerations.

7.8. Deviation(s) from statistical plan

Any deviations from the statistical plan will be documented in the clinical investigation report.

8. Data management

8.1. Data review, database cleaning, and issuing and resolving data queries

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

To ensure correct data entry, data is entered twice (double data entry). Data management is responsible for control of data consistency and for completeness of data from each subject.

Discrepancies are listed in Data Query Forms (DQF), and the Investigator is responsible for solving these promptly. When all DQFs are solved the database is locked and the statistical analyses are performed.

8.2. Verification, validation and securing of electronic clinical data systems

EXPeRT Data Management, version 5.0.05 system delivered by OmniComm Systems Inc. is used for data management. The system is designed to be compliant with the requirements of 21 CFR part 11. It is a validated data management system allowing only qualified and trained personnel to enter the system.

8.3. Data retention

The sponsor file must be archived for a minimum period of 5 years after the final clinical investigation report has been signed.

All investigation site documents must be archived for a minimum period of 5 years after the final clinical investigation report has been signed. The monitor is responsible for informing the investigator and the CTM if this period should be longer for their sites per local regulation.

9. Amendments to the CIP

Any significant changes to the CIP are:

- Agreed between sponsor, PI(s) and the coordinating investigator.
- Justified in a statement included in the amended section and the version number and date of amendment must be documented.
- Registered in the Change Log.
- Notified to or approved by the EC before implementation
- Notified to or approved by the regulatory authorities before implementation

Example of significant change: Changes of inclusion criteria, end points or assessment methods.

10. Clinical Investigation Plan deviations

10.1. Deviations

Deviations to Clinical Investigation Plan occurs when the activities during the clinical investigation diverge from the EC approved investigation plan.

A deviation does not increase risk or decrease benefit or; does not have a significant effect on the subject's rights, safety or welfare; and/or on the integrity of the data.

Examples of deviations:

- Vital signs obtained prior to informed consent
- Partly completing required tests

The Investigator is not allowed to deviate from the CIP unless under emergency circumstances and to protect the rights, safety and well-being of the subject(s).

Deviations must be reported to sponsor and deviations affecting the scientific aspect of the investigation or the safety of the subject is reported to the EC by sponsor.

10.2. Violations

Violations to the Clinical Investigation Plan occurs when there is divergence from the EC approved investigation plan (a deviation) that also:

- Reduces the quality or completeness of the data
- Impacts a subject's safety, rights or wellbeing

- Affects the scientific integrity

Examples of violations:

- Inadequate informed consent
- Enrolment of subjects not meeting the inclusion / exclusion criteria
- Initiation of study procedure prior to completion of informed consent
- Unreported SAE's
- Repeated deviations of the same nature
- Falsification

If any deviations and/or violations to the investigation plan are detected, the Clinical Manager will complete a Deviation/Violation Form and inform/discuss with the Principal Investigator immediately.

In case of continued or repeated violations affecting the scientific aspect of the investigation or the subjects' rights, safety and well-being sponsor will disqualify the PI from further participation in the investigation. The Clinical Manager must report all violations detected during a monitoring visit in the Periodic Monitoring Report.

11. 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 per 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 Investigator or a representative hereof 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).
- Subject identification.

12. Statement of compliance

The clinical investigation is conducted in accordance to:

- Ethical principles that have their origin in the Declaration of Helsinki, 1964, Last amended at the 64th WMA General Assembly, Brazil, 2013.
- MDD 93/42/EEC as amended by Directive 2007/47/EC (commonly known as the Medical Device Directive).
- ISO 14155:2011 "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.

12.1. 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.

12.2. Data protection

This clinical investigation does not require approval by the Data Protection Agency. Per the Order 410 of 09/05/2012, Exemption from submission to the Data Protection Agency, handling of sensitive personal data in health science research projects is exempted from the requirement for notification and permission from the Data Protection Agency if the project is covered by the Act on Scientific Ethics of Health Science Research Projects and is authorized by a Scientific Committee.

Coloplast A/S is committed to and follows the Data Protection Act. All information collected during this investigation is kept strictly confidential. Subjects are identified by an investigation number and the investigation monitor has limited access to subjects' documentation for source data verification. Any information which could identify a subject remains with the investigator where it is archived with investigation documents. Subjects remain anonymous for data analysis.

Should the investigation require future review, relevant regulatory authorities and ethics committees will be allowed access to all relevant information for audit and inspection purposes.

12.3. Indemnity

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

[redacted]

12.4. Financial conditions

The investigation is initiated and sponsored by Coloplast A/S.

Coloplast pays the salary for the clinical staff in Denmark and for all investigation materials. The investigation expenses are expected to amount [redacted] per subject. The investigator is employed by Coloplast A/S, thus a Disclosure of Conflicts of Interests will be filled out before initiation of the investigation. An external nurse will be in-sourced to conduct the visits together with Coloplast personnel.

Subjects will be paid for their participation in the study and receives a gift voucher equivalent in value to [redacted] per visit. The gift is taxable (B-tax) and the subjects is responsible for reporting this.

13. 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 have a minimum of 24 hours 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 Investigator or a representative hereof 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. Clinical Manager 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.

In addition, subjects will be asked to sign a Letter of Authority, and sign a consent form if they agree to participate in interview. The consent to interview includes consent to tape recording and filming during the interviews. However, the subject can participate in interviews without this.

Confidentiality Agreement

In this investigation, there will be a Confidentiality Agreement between the subject and Coloplast A/S.

At Coloplast, the aim is to involve the user in testing of improved catheters as early as possible. To develop a better product, it is essential for Coloplast A/S to get the user's wishes and comments to the new products as early as possible.

Furthermore, it is important for Coloplast to ensure that any new inventions can be patented. To obtain a balance between involving the user at a very early stage and at the same time not waive the rights that Coloplast possess, it has been decided to ask the participants to treat the products and the material they receive from Coloplast in a confidential way.

The confidentiality only concerns the physical materials and products, which are delivered by Coloplast and it does not in any way influence other aspects of the user's rights.

The primary purpose of the confidentiality is to ensure that a possible breach of contract will fall under the Danish Patent Act §2(2) and thereby ensure that Coloplast still has the possibility to obtain a patent, and for Coloplast it is not common practice to initiate court cases based on any minor breach of contract.

14. Adverse events, serious adverse events and device deficiencies

14.1. Adverse events

14.1.1. Adverse event

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 related to the medical device(s), or the procedures involved. This could include events such as headache or dizziness.

14.1.2. 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, malfunction of the device, use error or from intentional misuse of the device.

Table 5 Anticipated adverse device effects and their likely incidence rates

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

Incidence rates for patients are based on literature data (2, 3) while rates for healthy volunteers are based on data from a clinical study (4). Definition of incidence rates are based on Coloplast risk management system (very unlikely 0-1%, unlikely 2-10%, occasional 11-50%, likely 51-90%, very likely 91-100%).

14.2. Device deficiency

A device deficiency is the inadequacy of the investigational medical device with respect to its identity, quality, durability, reliability, safety or performance. This includes malfunctions, misuse or use errors and inadequate labelling.

14.3. Serious adverse events

14.3.1. Serious adverse event

A serious adverse event is an adverse event that:

- Led to death,
- Led to a serious deterioration in health of the subject that either resulted in:
  1) a life-threatening illness or injury, or
  2) a permanent impairment of a body structure or a body function, or
  3) required in-patient hospitalization or prolongation of existing 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.

14.3.2. Serious adverse device effect

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

14.3.3. Anticipated serious adverse device effect

There are no anticipated serious adverse device effects.

14.3.4. Unanticipated serious adverse device effect

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.

14.4. 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.

Subjects are informed to contact investigator if any adverse event should occur during the investigation. Furthermore, investigator will inform the subjects to contact him should serious adverse events occur within one week of the subject is terminated from the study. Subjects are informed to contact their general physician in case of any adverse event(s) happening later than one week of investigation termination.
The status of all ongoing adverse events is documented during site close-out.

14.5. Reporting and timelines

14.5.1. Investigators 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 three calendar days.
- 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 three calendar days.
- New findings and/or updates in relation to already reported serious events should also be reported to sponsor within three calendar days.
- Device deficiencies and all adverse device effects must be reported to sponsor within 10 days.

All above events must be reported by use of the relevant adverse event/serious adverse event/device deficiency form.

Please report to: **VIGILANCE@coloplast.com**
In cases where a mail is not reachable, please call [redacted].

14.5.2. Sponsors reporting responsibilities

It is the responsibility of sponsor to ensure that the following are reported to the relevant authorities immediately, but no later than seven 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 two calendar days after awareness by sponsor report the event to national regulatory authorities.

15. 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 ethic committee.

If monitoring or auditing of the clinical investigation identifies serious or repeated deviations at the participating investigation sites, sponsor will suspend or terminate the investigation site. The sponsor or investigator will inform the regulatory authority as appropriate and notify the ethics committee 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.

16. 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 coordinating investigator must sign the final version of the clinical investigation report or an affidavit, indicating their agreement with the contents. If no coordinating investigator is appointed, then the signatures of the principal investigator(s) should be obtained.

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

17. Publication policy

In connection with the publication policy Coloplast 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 on a public 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 public 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 protocol 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.

The results may be submitted to a scientific journal.

18. Bibliography

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