Clinical Investigation Plan

CP279

SpeediCath® with newly developed swelling media

Clinical study in healthy volunteers evaluating the performance and handling of a urinary intermittent catheter with a newly developed swelling media.

August 2019 – March 2020

Master

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[redacted]

CHANGE LOG

VERSION NUMBER	ISSUED BY *(INITIALS)*	COMMENTS (MAJOR CHANGES SINCE LAST REVISION)
1.0	[redacted]	Document established in template version 3.0 This CIP was based on Clinical Study Agreement, SpeediCath® Upgrade 2.0 VV-0197022
2.0	[redacted]	"Coating and swelling media" changed to "lubricated coating". Table 3 added. "Subject registration of overall discomfort during catheterisation (VAS)" added in table 8. Minor editorial changes
3.0	[redacted]	Due to feedback from EC the following has been updated: Section 6.1: Coloplast has taken the initiation to the study Section 12.4: The remuneration is taxable (B-income) and it is the responsibility of the subject to declare this to Skat.
4.0	[redacted]	Update due to study start up delay and due to that the test catheters will not be CE marked before study start up. Study period changed from aug2018-sep2018 to aug2019-mar2020 BBT has been renamed to "newly developed swelling media" Clinical manager updated Scientific manager updated Label updated Version 4.0 was not submitted to EC
5.0	[redacted]	Final report date changed to March2021

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> SYNOPSIS OF THE CLINICAL INVESTIGATION

Objectives

The aim of the study is to evaluate safety and performance of a SpeediCath® Catheter with a newly developed swelling media for urinary intermittent catheters in healthy volunteers. The comparator catheters in this investigation are SpeediCath® Standard Male catheters.
The primary objective of the study is to show that SpeediCath® with the new swelling media, being the investigational device, are non-inferior (no worse) to the CE-marked SpeediCath® Standard Male catheters with respect to overall discomfort during catheterisation.

Primary endpoint and secondary endpoint(s)

Primary endpoint:
The primary endpoint is evaluation of overall discomfort during catheterisation measured by the Visual Analogue Scale (VAS).

Secondary endpoints:

- Discomfort during insertion and withdrawal
- Discomfort during urination post catheterisation
- Handling during insertion and withdrawal, including need to touch the coated part of the catheter
- Visual blood during catheterisation
- Microscopic Haematuria (non-visual blood in urine)
- Adverse events

Pass/fail criteria

The average discomfort score of the investigational device during catheterisation must not exceed the average discomfort score of the SpeediCath® with more than 1.2 cm on the VAS (10cm).

Design of the investigation

The investigation is conducted at one site. The study is a single blinded, randomised, crossover study including 22 healthy men, each catheterised two times with 4-15 days between the catheterisations. Nurses will perform the catheterisation. As there is a visual difference in the products, it is only possible to blind the subjects. A cross-over design has been chosen over a parallel design to minimise interpersonal variation. A lower number of subjects are required with this study design as each subject act as his own control. To minimize carry-over effect 4-15 days between the two catheterisations is required. All subjects will be catheterised with both catheters. The order of the catheterisations will be randomised to prevent bias.

Population

The investigational population consists of 22 healthy male volunteers who comply with the following inclusion and exclusion criteria:

[redacted]

Inclusion criteria:

1. Have given written informed consent
2. Be at least 18 years of age and have full legal capacity
3. Be a male
4. Willing to refrain from using analgesics up to 24 hours prior to catheterisation visits
5. Have a negative urine multistix - erythrocytes (Microscopic haematuria)
6. Have a negative urine multistix:
    - Leukocytes
    - Nitrite

    Or if positive, subsequent negative for bacterial growth in urine culture

Exclusion criteria:

1. Abnormalities, diseases or surgical procedures performed in the lower urinary tract
2. Symptoms of urinary tract infections (at least one of the following: frequent urination, stinging or pain at urination)
3. Participating in other clinical investigations related to urinary tracts system during this investigation (inclusion to termination) or have previously participated in this investigation
4. Known hypersensitivity toward any of the investigational device

Investigational device

The investigational device is a non-CE marked class I, sterile catheter intended for intermittent catheterisation of the bladder through the urethra. The difference between the investigational device and the comparator, CE-marked SpeediCath®Standard,Male, is the swelling media.

All catheters in the investigation are CH12, 40cm, Male, Nelaton.

Investigation approval

The investigation shall be approved by the Ethics Committee of the Capital Region of Denmark and by the Danish Medicines Agency, Lægemiddelstyrelsen, before the investigation is initiated.

[redacted]

All parties declare by their signature on the electronic and separate signature page to follow the Clinical Investigation Plan CP279 in accordance with the Declaration of Helsinki, ISO 14155 and the Medical Device Regulative.

SPONSOR

Coloplast A/S

Holtedam 1

DK - 3050 Humlebæk

Denmark

+45 4911 1111

[redacted]

1. List of personnel involved in the investigation

1.1. Sponsor representatives

CLINICAL MANAGER	SENIOR STATISTICIAN
[redacted]	[redacted]
DATA MANAGER	**VICE PRESIDENT, MEDICAL AFFAIRS**
[redacted]	[redacted]
SCIENTIFIC MANAGER	
[redacted]	

In case of emergency, please contact the Clinical Manager

1.2. Investigators

One site is included in the study.

INVESTIGATIONAL SITE – 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.

[redacted]

2. Identification and description of the investigational device

The investigational device is a non-CE marked intermittent catheter, class Is, medical device, as defined by the European Communities' Council Directive 93/42/EEC and amendments

2.1. Manufacture

The investigational device will be manufactured at the following manufacturer:

[redacted]

2.1.1. Identification, traceability and labelling of the device

The investigational device will be labelled on individual product and retail box for identification and traceability as shown in figure 1.

Figure 1 Labelling of the investigational device.

2.1.2. Intended purpose of the device in the clinical investigation

The investigational device is a urinary catheter for intermittent use. The catheter is inserted into the urethra until the bladder is reached. Once the bladder is emptied, the catheter is withdrawn.

There are no proposed contraindications.

[redacted]

2.1.3. Intended population for the device

The intended population in the investigation is healthy men. For details and justification of choice of population please see section 6.3.

2.1.4. Description of the investigational device

The investigational device is a ready-to-use coated catheter for intermittent use (Figure 2).

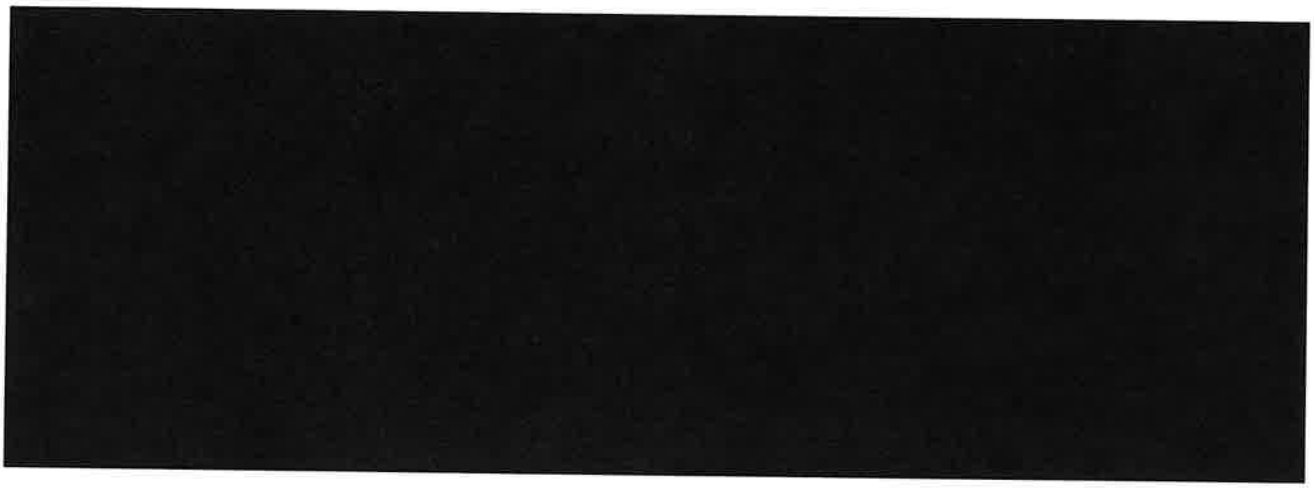

Figure 2: Investigational device

The investigational device is coated with hydrophilic polymers. Each catheter is packed in a foil pouch containing an aqueous solution which serves to hydrate the coating and thus to reduce surface friction of the catheter. This solution is termed the swelling media.

Investigational device: SpeediCath® Standard Male with newly developed swelling media.
Comparator: SpeediCath® Standard Male, with existing swelling media.

The only difference between the investigational device and the comparator, lies in the newly developed swellingmedia.

The investigational device resembles the comparator, however, there are small visual/tactile differences why the products cannot be blinded for the nurses (colour of the catheter and swelling media).

The catheter tubes of both devices are made of polyurethane and are both Nelaton catheters (straight) for males, CH 12 in diameter (4.0 mm), approximately 40 cm in length, including connector.

The investigational device is packed the same way as the comparator: Each catheter is packed individually in a foil. Thirty of these are packed in a cardboard box and sterilised using e-beam according EN556. Each box contains an instruction for use (IFU).

2.1.5. Handling and training

The handling of the investigational device is described in details in the IFU. The investigational device is to be handled the same way as the comparator which the study nurses are experienced in using.

[redacted]

2.1.6. Comparator product

The CE-marked SpeediCath® Standard Male, is used as the comparator product as it is similar to the investigational device except for the newly developed swelling media. SpeediCath® Standard Male is packed in retail boxes of 30 pieces with an IFU. In addition to the existing labelling, the product will be labelled with the following text:

3. Justification for conducting the clinical investigation

Intermittent catheterisation is the preferred method of bladder emptying for persons with spinal cord injuries and neurogenic bladder dysfunction. Coloplast manufactures different catheters for intermittent catheterisation and markets these worldwide.

SpeediCath® Standard is an intermittent catheter that has been on the market for many years and Coloplast has now developed a new swelling media for the catheter. The swelling media, ensures [redacted] during insertion and withdrawal of the product. This clinical investigation may enable future development within swelling coating and swelling media technology with benefits for the user like minimizing excess solution for saturating the coating.

4. Ethical considerations, 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 and society.

4.1. Anticipated benefits

By participating in this investigation, the subjects will contribute with important information for developing a new catheter swelling media that in turn may benefit individuals who are dependent on catheters for emptying of their bladder.

4.2. Anticipated risk, side effects and disadvantages

The potential risks associated with the use of a urinary catheter have been assessed in the risk assessment in accordance with DS/EN ISO 14971:2012. Catheterisation might produce stinging, discomfort or micro trauma in the urethra. The investigational device is not expected to produce more stinging or discomfort compared to any other standard catheter on the market.

4.3. Possible interactions with concomitant medical treatments

There is no known interaction between the use of catheters and concomitant medication.

4.4. Benefits versus risks

The clinical investigation is conducted in accordance with "The Declaration of Helsinki, 1964, last amended at the 64th WMA General Assembly, Brazil, October 2013". Subjects will by participating in this investigation contribute with important information for developing new catheter swelling medias with benefits for the user like minimizing excess solution for saturating the coating.

[redacted]

The risks and disadvantages of participating in the investigation are estimated to be low. The healthy subjects will not have any benefits from this investigation, but catheter users may in the future benefit from a new and improved swelling media of the catheter.

4.5. Other ethical considerations

As the subjects are healthy men who are not dependent on catheters for emptying their bladder, they will not themselves benefit from any potential new catheter on the market. Should the subjects be interested in the results of the study, these can be accessed via a public database, this is described in the written information given to the subjects prior to entering the investigation.

5. Objectives and hypotheses of the clinical investigation

5.1. Objectives

The primary objective of the study is to show that SpeediCath® with the new swelling media, being the investigational device, are non-inferior (no worse) to the CE-marked SpeediCath® Standard Male catheters with respect to overall discomfort during catheterisation.

The secondary objective is to compare performance and handling of the investigational device with the CE-marked SpeediCath®Standard Male. For more details see section 6.1.

5.2. Hypotheses

The average discomfort score of the investigational device with the new swelling media during catheterisation must not exceed the average discomfort score of the SpeediCath®Standard Male with more than 1.2 cm on the VAS (10 cm). This hypothesis will be examined statistically.

5.3. Risks and anticipated adverse device effects to be assessed

All adverse events which may occur are assessed by the investigator. Please refer to section 14, regarding adverse events.

6. Design of the clinical investigation

6.1. General

Coloplast A/S has taken the initiative to this study. The clinical investigation consists of a randomised, single-blinded, cross-over study period, conducted at a single site.

Table 1 illustrates the design of the clinical investigation. Study period is cross-over with two products. Detailed description of visits and corresponding assessments are given in section 6.4.4.

Visit	Investigation period	Days to next visit
	Study period	
0	Inclusion	0-7
1	Catheterisation with randomised product 1	4-15
2	Catheterisation with randomised product 2	(last visit)

Table 1: Study period.

[redacted]

22 subjects will be included. Each subject will be catheterised once with each of the two catheters in a randomised order. There must be a minimum of 4 days and a maximum of 15 days between each catheterisation. This is to ensure that if a catheterisation has caused urethral micro trauma the micro trauma will heal up before next catheterisation minimum 4 days later. The maximum of 15 days is due to logistical reasons. Each subject will be included in the study period for 5-23 days (not including time for deciding whether to participate or not, see informed consent process section 13).

Table 2 illustrates the study period.

Visit	Process	Activity
Information	Study Information	• Subject information
0	Inclusion	• Informed Consent Form • In- and exclusion criteria fulfilled • Multistix performed (leukocytes, Nitrite and erythrocytes) • Randomisation • Concomitant medication • Schedule visit 1 (may be same day as visit 0)
1	Catheterisation with randomised product 1	• Check for symptoms of UTI and use of analgesics • Urine sample from subject to measure microscopic haematuria, before catheterisation • Catheterisation with randomised product 1 • VAS registered by subject, during insertion, after catherisation (primary) and again after first urination post catherisation (secondary) • CRF questions to nurse • Urine sample from subject to measure microscopic haematuria, after catheterisation • Registration of any adverse events and concomitant medication • Schedule visit 2
2	Catheterisation with randomised product 2	• Check for symptoms of UTI and use of analgesics • Urine sample from subject to measure microscopic haematuria, before catheterisation • Catheterisation with randomised product 2 • VAS registered by subject after catherisation (primary) and again after first urination post catherisation (secondary) • CRF questions to nurse • Urine sample from subject to measure microscopic haematuria, after catheterisation • Registration of any adverse events and concomitant medication • Termination form

Table 2: Study period including three visits.

The study period lasts approximately 1 month.

[redacted]

6.1.1. Primary endpoint

The primary endpoint is evaluation of overall discomfort during catheterisation measured by the Visual Analogue Scale (VAS).

After catheterisation, the subject is asked to evaluate the overall discomfort of the catheterisation. The subject marks his evaluation as a vertical line on a 10cm horizontal VAS scale ranging from "no discomfort" to "worst possible discomfort" caused by the catheter.

Section 7 describes the statistical analysis to be performed on the primary endpoint.

Primary endpoint is given in Table 3

Primary endpoint Assessed at visit 1-2	Type of assessment	Assessed by
Overall discomfort during catheterisation	VAS After catheterisation, the subject is asked to evaluate the overall discomfort of the catheterisation. The subject marks his evaluation as a vertical line on a 10cm horizontal VAS scale ranging from "no discomfort" to "worst possible discomfort" caused by the catheter.	- Completed by subject in the CRF (10 cm horizontal line) - Measured and entered with a score in the CRF by the Investigator/ study nurse

Table 3 Primary endpoint

[redacted]

6.1.2. Secondary endpoints

Secondary endpoints are given in Table 4.

Secondary endpoint Assessed at visit 1 and 2	Type of assessment	Assessed by
Discomfort measured during: Insertion	VAS On a scale ranging from "no discomfort" to "worst possible discomfort comfort" caused by the catheter, set a vertical line indicating how you experienced the insertion of the catheter	- Completed by subject in the CRF (10 cm horizontal line) - Measured and entered with a score in the CRF by the Investigator/ study nurse
Withdrawal	On a scale ranging from "no discomfort" to "worst possible discomfort comfort" caused by the catheter, set a vertical line indicating how you experienced the withdrawal of the catheter	
Handling during: Insertion	5point scale - How did you experience insertion of the catheter? - Very difficult – difficult – neither difficult nor easy – easy – very easy	By the Investigator/study nurse and entered in the CRF
Withdrawal	5point scale - How did you experience withdrawal of the catheter? - Very difficult – difficult – neither difficult nor easy – easy – very easy	
Need to touch the coated part of the catheter during insertion	No/Yes	
Visual blood	No/Yes - Did you experience visual blood during Catheterisation (Yes/No) If yes, where was the blood located? On the tip – at the eyelets – on the whole catheter – in the urine Several answers accepted	By the Investigator/study nurse and entered in the CRF

[redacted]

Discomfort during urination post catheterisation	VAS - On a scale ranging from "no discomfort" to "worst possible discomfort" set a vertical line indicating how you experienced urination	- Completed by subject in the CRF (10 cm horizontal line) - Measured and entered with a score in the CRF by the Investigator/ study nurse
Urinary analysis Microscopic haematuria (erythrocytes), before and after each catheterisation	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 positive	By the Investigator/study nurse and entered in the CRF
Adverse events	-	Assessed and entered in the CRF by Investigator

Table 4: Secondary endpoints

Section 7 describes the statistical analysis to be performed on the secondary endpoints.

6.1.3. Rationale for the selection and measurement of endpoints

Endpoints have been chosen in order to evaluate the performance and handling of the investigational device and match endpoints used in earlier studies with intermittent catheters (DK058CC Danish Health Authority journal number 8313-39 and Ethics Committee journal number H-D-2008-122; CP063CC SST journal number 8313-60 and Ethics Committee journal number H-2-2009-127 and CP235: Danish Medicine Agency journal number 2012122585 and Ethics Committee journal number H-3-2012-173: CP269: Danish Medicine Agency journal number 2016071463 and Ethics Committee journal Number H-16033335).

Some catheter users experience discomfort when catheterising. The main purpose of this clinical investigation is to evaluate whether the investigational device is non-inferior (no worse) to the comparator, with respect to discomfort. Therefore, the primary endpoint is evaluated using VAS, which is a well-known method for clinical use. This subjective method enables an evaluation of the [redacted] coating in relation to discomfort, which would not necessarily be apparent in visual parameters as bleeding.

Secondary endpoints are chosen to support the evaluation of performance as well as to evaluate whether the new developed swelling media affects handling of the catheter.

[redacted]

6.1.4. Discussion of the clinical investigation design

A cross-over design has been chosen over a parallel design to minimise the interpersonal variation. Fewer subjects are required with this study design as each subject act as his own control. There might be a carry-over effect which is why there must be a period of 4-15 days between each test day to ensure that potential microtrauma from the first catheterisation has healed. The order of catheters used is randomised to minimise bias.

During the investigation period, it is not possible to blind the study nurses performing the catheterisations, however, when quantitative data is collected the subjects are blinded to the catheters by a curtain.

6.2. Investigational device and comparator(s)

During the study period, each subject will be exposed to one catheterisation with the investigational device, and one catheterisation with the comparator.

	Investigational device (# of products)	Comparator (# of products)
Study period	22	22

Table 5: Overview of products needed in the study period

Each catheterisation lasts approximately 15 minutes totally.

A total of 22 of investigational device products and 22 comparator products are needed for the study period shown in table 5. However, to ensure that the site has enough products, 75 of each product will be provided by Sponsor to the site. All products will be accounted for, see section 11.

Supplementing devices or instruments normally used for catheterisation (e.g. medical gloves, tray for urine collection) are supplied by investigator. Urine bags may 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 catheters as this may affect the data.

6.3. Subjects

To be included in the investigation, the subjects must comply with the inclusion criteria and not with the exclusion criteria described in section 6.3.1 and 6.3.2. A randomisation will take place before entering the study.

6.3.1. Inclusion and Exclusion criteria for subject selection

Subjects interested in participating in the clinical investigation must comply with the criteria described in table 5 below.

Inclusion Criteria:	Justification for inclusion criteria:
1. Have given written informed consent and signed letter of authority	1. To ensure voluntarily and that the Helsinki declaration is met.

[redacted]

2. Be at least 18 years of age and have full legal capacity	2. To meet the Helsinki declaration
3. Be a male	3. Only males are included as their anatomy is considered 'worst case' due to a longer urethra.
4. Willing to refrain from using analgesics[1] up to 24 hours prior to catheterisation visits	4. Pain relief could affect the primary and secondary endpoints of discomfort
5. Have a negative urine multistix - erythrocytes (microscopic haematuria)	5. Haematuria is included in the study as it is a secondary endpoint. If a subject has haematuria at study start it could affect evaluation of data.
6. Have a negative urine multistix: - Leukocytes - Nitrite or if positive, subsequent negative for bacterial growth in urine culture (only conducted if positive leukocyte/nitrite multistix)	6. To ensure the subject does not have a urinary tract infection at inclusion
Exclusion Criteria:	**Justification for exclusion criteria:**
1. Abnormalities, diseases or surgical procedures performed in the lower urinary tract	**1.** To ensure a homogeneous group of urinary tracts where abnormalities, diseases or surgical procedures do not influence on the subject's perception of the test catheters.
2. Symptoms of urinary tract infections (at least one of the following: frequent urination, stinging or pain at urination)	2. To ensure the subject does not have a urinary tract infection at inclusion
3. Participation in any other clinical investigations related to urinary tract system during this investigation (Inclusion → termination)	3. Other investigational procedures may interfere with the endpoints of this investigation
4. Known hypersensitivity toward any of the investigational device	4. Ethical reasons and to avoid bias with respect to assessment of the endpoints

Table 6: In- and Exclusion criteria and adherent justification

To determine discomfort, it is necessary to have normal sensation in the urinary tract, hence healthy subjects have been chosen.

The subject may not use analgesics 24 hours prior to catheterisation visits as discomfort is measured as endpoints and to ensure an optimal for investigator/investigator representatives.

Leucocytes or nitrite may be present in the urine of healthy individuals (without urinary tract infection). In these cases, a subsequent analysis for bacterial growth in urine culture will indicate whether there is a presence of

[1]Medicines for systemic use that are pain relieving without significantly affecting the consciousness

[redacted]

bacteria in the urine. This is normal hospital procedure. This analysis will be conducted at [redacted]

6.3.2. Recruitment and enrolment

Recruitment of potential subjects will begin once approval has been obtained from the Ethics Committee and the Danish Medicine Agency

Recruitment will take place using subject records from the site as well as via www.forsøgsperson.dk and, if necessary, through advertisements in local newspapers and educational institutions.
Before the investigation starts, investigator and all study nurses will receive verbal information about the investigation, as well as instruction on investigation procedures and completion of the CRF. Before the investigation can begin at a site, the investigator must sign the current Clinical Investigation Plan to declare that he will conduct the investigation according the plan.

Subjects recruited via subject records

Investigator identifies potential subjects in relation to in- and exclusion criteria through subject records kept at the site (from previous clinical studies involving healthy subjects). The identified potential subjects will receive by mail or e-mail the Subject Invitation Letter attached the written subject information and "Forsøgspersoners rettigheder i et sundhedsvidenskabeligt forskningsprojekt". If the subject is interested in participating, he is encouraged to contact the site and visit 0 is arranged (informed consent process, see section 13).

Subjects recruited via www.forsøgsperson.dk, local newspapers or educational institutions

Subjects may furthermore be recruited through www.forsøgsperson.dk where potential subjects can gather information on clinical studies. If necessary, they may also be recruited through local newspapers and educational institutions. Interested potential subjects will contact the Clinical Manager [redacted] or a representative hereof. In- and exclusion criteria are preliminary reviewed and general questions regarding the study are answered. If the potential subject is interested in participating, he will receive the written subject information and "Forsøgspersoners rettigheder i et sundhedsvidenskabeligt forskningsprojekt" and contact information is passed on to the investigator or study nurse, who will then contact the potential subject. If he still wishes to participate, visit 0 is arranged.

Potential subjects recruited in one of the above ways will, at visit 0, go through the informed consent process (see section 13). Once enrolled in the study, the subject may then continue to formal in- and/or exclusion.

6.3.3. 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 withdraw a subject from the investigation at any time if he assesses withdrawal to be in the subject's best interest.

The investigator must withdraw a subject from the investigation for the following reasons:

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

Withdrawn subjects will not be replaced by new subjects.

[redacted]

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

At termination, due to above reasons investigator or study nurse completes the termination form and sponsor is informed.

6.3.4. Point of enrolment

A subject is considered enrolled in the investigation when he has signed and dated the Informed Consent Form.

The expected duration of involvement for each subject is described in section 6.1.

6.3.5. Total expected duration of the clinical investigation

The dates in table 7 below are approximate. No subjects will be enrolled before the required approval has been obtained from the Ethics Committee of the Capital Region of Denmark and Lægemiddelstyrelsen. The same committees will be informed of investigation termination within 90 days hereof (unless the investigation is terminated prematurely where information is then given 15 days after termination, including the reason for the premature termination).

Activity	Estimated time
First subject enrolled	August 2019
Last subject enrolled	February 2020
Last subject completed	March 2020
Final Report	March 2021

Table 7: Estimated timeline

6.3.6. Total number of subjects

During the investigation period, there will be enrolled 22 subjects based on a drop-out rate of 20%. A subject is considered enrolled in the investigation when he has signed and dated the Informed Consent Form.

6.4. Procedures

6.4.1. Clinical investigation-related procedures

Before initiation of the clinical investigation, the sponsor is provided with key personnel's current signed and dated CVs to verify their qualifications. Key site personnel are those who treat or evaluate subject data in the clinical investigation. The sponsor will ensure that all site personnel are trained in using the investigational device as well as in the investigation procedures, how to complete the CRFs, the procedure for reporting an adverse event or serious adverse event (how, when, to whom), and who to contact in the case of an emergency related to the investigational device.

[redacted]

Study period

During the study period, each subject has three visits: visits 0, 1 and 2. Visit 0 (inclusion) and visit 1 can be the same day, as follows:

Visit 0 (Inclusion):

Subject will be given information about the investigation and will sign the Informed Consent Form and the Letter of Authority (see section 13). It is ensured that in- and exclusion criteria are met, including urine analysis (leukocytes, nitrite and erythrocytes) with multistix (Multistix 7, Siemens).

Enrolled subjects are allocated a subject number, and will hereafter be randomised per the study design and demographics, baseline data and concomitant medication is recorded.

Visit 1 (0-7 days after visit 0):

Subject is asked about symptoms for urinary tract infections and use of analgesics up to 24 hours prior to the visit. An urine sample is collected, and microscopic haematuria is measured before catheterisation is initiated. If the subject presents negative for urinary tract infections, use of analgesics and microscopic haematuria, the subject will be catheterised with product 1 per randomisation. The subject is offered something to drink and then asked for a urine sample to measure if any microscopic haematuria is present.
The nurse registers relevant answers in the eCRF, including possible adverse events. In addition, subject registers the endpoints regarding discomfort (VAS-scale) during catheterisation and again after first urination and the nurse measure and enters the subject's assessments in the eCRF. Next visit is scheduled.

Visit 2 (4-15 days after last visit):

The procedure for visit 1 is repeated in visit 2.

After completed procedure, the termination form will be completed by investigator or study nurse.
If the subject develops symptoms of urinary tract infection or has visual blood in the urine during the investigation he will be treated per standard hospital procedure.
It is not considered necessary to have a follow-up period after the study period. The subject will be instructed to contact investigator should he experience discomfort or other problems after the study. If investigator believes it is necessary to follow up on a subject it will be registered in the eCRF.

6.4.2. Activities performed by sponsor representatives

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

- Training of investigator and study nurses in the study procedures, how to use the products, complete the eCRF and how to report possible safety issues to Sponsor. All training will be documented by site and sponsor by signing a Training Log
- Support during the recruitment process
- Monitoring

6.4.3. Foreseeable factors that may compromise the outcome/results

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

Flow chart

[redacted]

Error! Reference source not found.8 shows the scheduled visits and corresponding assessments for the study period

Activity	Visit 0 (Inclusion)	Visit 1	Visit 2
Oral and written information	X		
Informed Consent Form	X		
Check of inclusion and exclusion criteria, including urine analysis	X		
Demographic and baseline data	X		
Allocation of subject number	X		
Randomisation	X		
Question subject about symptoms of UTI before Catheterisation		X	X
Question subject about use of analgesics 24 hours prior to Catheterisation		X	X
Urine sample for measuring endpoints (before catheterisation)		X	X
Catheterisation per Randomisation		X	X
Subject registration of overall discomfort during catheterisation (VAS)		X	X
Subject registration of discomfort during insertion and withdrawal of the catheter (VAS)		X	X
Urine sample for measuring endpoints (after catheterisation)		X	X
Subject registration of discomfort during micturition (VAS)		X	X
Nurse registration of endpoints, including results of urine analysis		X	X
Concomitant medication		X	X
Product accountability		X	X
AEs/ADEs/SAEs/SADEs*		X	X
Termination form**			X

Table 8 Study period: Scheduled visits and corresponding assessments.

*Registered continuously. **The Termination Form is filled out when the subject leaves the investigation, could be prior to visit 2.

6.4.4. Randomisation procedure

Each subject will be allocated randomly into one of two possible treatment sequences for the study period. Subjects are allocated to a randomisation number per a randomisation list generated automatically by computer (SAS, version 9.4).

At visit 0 investigator or his representative brakes a sealed, non-transparent envelope with the randomisation block inside. Randomisation number is registered in the electronic Case Report Form (eCRF) by investigator or his representative. The randomisation list is archived in Sponsor File.

[redacted]

6.4.5. Blinding

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 primary and secondary endpoints regarding discomfort (VAS) during catheterisation and micturition. Haematuria is measured automatically by computers, hence eliminating possible bias.

6.4.6. Case Report Forms

Assessments and observations throughout the investigation for each subject and nurse will be carefully collected in the eCRF.
The eCRFs are supplied by the sponsor by a unique log on to the electronic Data Management System Rave EDC. Each eCRF is unique as it includes an identification number and is created for specifically for each subject. It is the responsibility of the investigator to ensure that all data are entered promptly and correctly.

The sponsor will be responsible for training the investigator and the study nurse in completion of the eCRF. The nurse will be responsible for guiding the subject on how to complete the subject's part of the CRF. The eCRF will clearly state which parts are to be completed by whom. The subject's part will be the pages regarding endpoints 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 enter the measurement in the eCRF.

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

6.5. Concomitant treatment

Subjects may not use analgesics 24 hours prior to catheterisation visits, see Inclusion and exclusion criteria section 6.3.1.

Subjects may not participate in other interventional clinical investigations during participation in this investigation.

6.6. Monitoring plan

Planning of monitoring visits and monitoring is carried out by the Clinical Manager or delegate.

Before doing any review of subject data, the Clinical Manager or delegate 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 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 (2) will be conducted as soon as possible after the completion of the first 11 subjects

Monitoring visit three (3) will be conducted as soon as possible after the completion of the last 11 subjects

[redacted]

Monitoring visit four (4), 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 during the investigation will be 100% verified for timely completion for all subjects enrolled in the investigation. 100% source data verification between the subject recorded VAS-scale in the eCRF and the measurement of the scoring completed by the investigator/relevant staff will be performed.

Investigation Site File shall be monitored for 100% completion per the Investigation File Requirement Checklist (sponsor ref. number VV-0201336)

Monitoring activities conducted by the clinical manager or delegate 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.

During the monitoring visits the Clinical Manager or delegate will monitor that labels at products, retail boxes and shipments boxes are intact and legible.

The Clinical Manager or delegate 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.

6.6.1. Source data verification

Source data are: the eCRFs, Informed Consent Forms and urine bacterial analysis.

All data collected can be directly entered in the eCRF. 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-0201338).

Only the investigator, delegated site personnel and the sponsor representatives (personnel within Medical Affairs/Clinical Operations) will have access to all the eCRFs.

6.6.2. 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

Intention to Treat (ITT), Safety and Per Protocol (PP) 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 randomized 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.

The **PP population** will be constituted by a subset of ITT subjects

[redacted]

- who fulfil the inclusion/exclusion criteria
- where the primary endpoint may be evaluated for at least one of the two test days
- who do not violate the protocol in a serious way affecting the primary endpoint on all visits

Any exclusion of patients from the PP population must be documented.

Individual endpoints/data points may be excluded from analysis, even though the corresponding subject belongs to the ITT/PP 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.

Analysis of the primary endpoint

The primary endpoint is overall discomfort during catheterisation measured by VAS.

The purpose of the primary statistical analysis is to compare the discomfort level for the investigational device with that of SpeediCath® Standard Male, and measure the estimated difference against the non-inferiority margin equal to 1.2 cm. This non-inferiority margin defines the maximum value that the investigational device must fall below to be non-inferior to SpeediCath®Standard Male.

Based on data from DK058CC, DK063CC, CP235 and CP269, the average VAS discomfort level in healthy subjects is estimated to be 2.3cm. A 50% increase in the VAS mean level corresponds to an absolute difference of 1.2 cm. Hence it should be demonstrated that the mean difference between the investigational device and SpeediCath® Standard Male is less than 1.2 cm (see also section 7.2).

Let $\mu_{\text{investigational device}}$ be the mean discomfort level for the investigational device, and let $\mu_{\text{SpeediCath®}}$ be the corresponding mean level for SpeediCath®.

Let the null hypothesis and the alternative hypothesis be defined as:

- H_0: $\mu_{\text{Testproduct}} - \mu_{\text{SpeediCath®}} > 1.2$ cm
- H_1: $\mu_{\text{Testproduct}} - \mu_{\text{SpeediCath®}} < 1.2$ cm

Non-inferiority will be demonstrated if H_0 is rejected.

A mixed model with subject included as a random component will be applied for the analysis. Treatment (investigational device and SpeediCath®Standard Male) and test day (1, 2) will be included as fixed effects and age will be included as a covariate. The contrast between the investigational device and the SpeediCath® Standard Male, as well as the 95% confidence intervals will be estimated.

If the upper limit of the 95% confidence interval for the difference between the investigational device and SpeediCath® Standard Male is below 1.2, H_0 is rejected and the success criterion is fulfilled.

The primary analysis will be based upon the ITT analysis set and the PP analysis set. Non-inferiority is met if this conclusion is made based on both analysis sets.

Analysis of the secondary endpoints

The secondary endpoints "discomfort during insertion", "discomfort during withdrawal" and "discomfort during urination post catheterisation" measured by VAS-scales will be analysed using a similar model as applied for the primary analysis. The contrast between investigational device and SpeediCath® Standard Male, as well as the 95% confidence intervals will be estimated, and a test of the hypotheses no difference between the investigational device and SpeediCath® Standard Male will be performed.

[redacted]

The endpoints "handling during insertion" and "handling during withdrawal" are assessed using ordinal 5 point scales. A proportional odds model with subject included as a random effect, and with treatment (investigational device and SpeediCath®Standard Male) and test day (1, 2) will be included as fixed effects and age will be included as a covariate. The odds ratio between the investigational device and SpeediCath®Standard Male as well as the corresponding 95% confidence intervals will be estimated, and a test of the hypothesis of no difference between treatments (corresponding to an odds ratio equal to 1) will be performed.

The dichotomous endpoints "need to touch the coated part of the catheter during insertion (Y/N)" and "visual blood during Catheterisation (Y/N)" will be analysed by a logistic regression model with treatment and test day as fixed effects, age is a covariate and subject is a random effect.

The negative/positive haematuria results from the urinary analysis will be analysed using a similar model as applied for the dichotomous endpoints "need to touch the coated part of the catheter during insertion (Y/N)" whereas the specific categories within positive/negative are summarised

The analysis of these endpoints will be based on the ITT population.

Adverse events will be summarized based on the safety population. Further details will be described in the statistical analysis plan.

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

7.2. Sample size

This is a non-inferiority investigation, with a non-inferiority limit of 1.2 cm.

Based on data from trials DK058CC (SST journal number 8313-39 and Ethics Committee journal number H-D-2008-122) and CP063CC (SST journal number 8313-60 and Ethics Committee journal number H-2-2009-127), CP235 (SST journal number 2012122585 and Ethics Committee journal number H-3-2012-173) and CP269(SST journal number 2016071463 and Ethics Committee journal Number H-16033335) the standard deviation of VAS discomfort associated with SC is assumed to be 1.6, and the within subject correlation to be 0.5. The average VAS discomfort level in healthy subjects using SpeediCath®Standard Male was estimated to be 2.3 cm. Based on Li et al[1] it is assumed that a 50% increase is considered clinical relevant. Therefore, the non-inferiority limit of 1.2 cm is considered reasonable.

The effective number of subjects needed to obtain 85% power to demonstrate that a investigational device is non-inferior to SpeediCath®Standard Male is 18. The power has been calculated under the assumptions of standard deviation and within subject correlation mentioned above, and that the distribution of VAS is assumed to be the same for the investigational device as for SpeediCath®Standard Male.

The primary analysis is performed on the ITT analysis set as well as the PP analysis set. With a drop-out rate at 20%, 22 subjects will be included.

7.3. Level of significance and power

For information regarding the power and the significance level, see section 7.2.

7.4. Drop-out

Based on previous investigations on similar subject population the drop-out rate is expected to be 20%.

[redacted]

7.5. Pass/fail criteria

The success criteria for a investigational device, is that non-inferiority to SpeediCath®Standard Male in relation to the primary endpoint discomfort (max difference in VAS of +1.2 cm) is demonstrated.

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 the 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 analysis is carried out by Medical Affairs, Coloplast A/S.

Data Management is responsible for control of data consistency and for completeness of data from each subject.

Discrepancies are listed on the Data Query Forms (DQF) and the investigator is responsible for resolving these promptly. When all DQFs are resolved, the database is locked and the statistical analyses are performed.

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

Rave EDC, version 2018.2.2, system delivered by Medidata Solutions Inc., is used for data management. 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.

8.3. Data retention

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

All investigation site documents must be archived for a minimum period of 10 years after the final clinical investigation report has been signed. The Clinical manager or delegate is responsible for informing the investigator if this period should be longer for their sites per local regulation.

9. Amendments to the Clinical Investigation Plan

Any significant changes to the CIP must be:

- Agreed between the sponsor and the Principal investigator
- Justified in a statement included in the amended section. The version number and date of amendment must be documented

[redacted]

- Registered in the Change Log
- Notified to or approved by the Ethical Committee of the Capital Region of Denmark and by the Danish Medicine Agency before implementation

Examples of significant changes include: changes to inclusion criteria, endpoints or assessment methods.

10. Clinical Investigation Plan deviations / violations

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
- Urine dipstick is completed, but not sent for formal urine analysis
- 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 are 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 or delegate 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.

[redacted]

The Clinical Manager or delegate 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 site until return of or disposal.

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

- Date of receipt.
- Identification of each investigational device (batch no./serial no./unique code).
- The expiry date
- The date(s) of use.
- Subject identification.

The same accountability procedure will count for the comparator product.

12. 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 64th WMA General Assembly, Brazil, October 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".
- Executive Order on Medical Devices no. 1263 of 15 December 2008 (Bekendtgørelse om medicinsk udstyr nr. 1263 af 15. december 2008)

12.1. Ethics committee and regulatory authorities

The CIP and/or other relevant documents are submitted to the appropriate EC and the Danish Medicine Agency. This clinical investigation will not begin until the required approval from this ethics committee and regulatory authority has been obtained. Any amendment to the protocol will be submitted to the same ethics committee and regulatory authority.

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 authorised by a Scientific Committee.

[redacted]

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

Coloplast A/S will compensate investigator and study nurses for their time and resources spent on the investigation (including overhead for the hospital and administrative costs) as specified in a sponsor investigator contract. [redacted] Investigator has no apparent conflict of interest.

[redacted]. This is to compensate for any inconvenience caused during the catheterisations, time used and travel expenses. The remuneration is taxable (B-income) and it is the responsibility of the subject to declare this to Skat.

13. Informed consent process

Written informed consent is obtained from all subjects participating in the investigation after thorough written and verbal information. The informed consent process takes place in a room reserved for ensuring privacy and quiet surroundings at the investigator's department. The subjects will receive both written and verbal information about the possibility of bringing a companion to the visit and to any possible subsequent visits.

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. If the subject wishes to consent immediately after receiving information, he may do so and in- and exclusion may be initiated.

The subjects will be informed that their participation is voluntary and that they may leave the investigation at any time, without this having any influence on their further treatment.

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

If new information is to be given during the investigation, sponsor will inform the investigators, and the new information is given to the subjects by the investigator. If new information becomes available that can significantly affect a subject's future health and medical care that information will be provided to the subject in writ-

[redacted]

ten form. The Clinical Manager or delegate 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.

14. Adverse events, serious adverse events and device deficiencies

14.1. Adverse event (AE)

An adverse event is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) that may occur in subjects, users or other parties, whether it is related to the medical device(s), or the procedures involved. This could include events such as headache or dizziness.

14.2. Adverse device effect (ADE)

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 to the medical device(s) on the adverse event form.

The definition of an adverse device effect includes any event resulting from insufficiencies or inadequacies in the instructions for use, malfunction of the device, user error or intentional misuse of the device.

Table 9 lists anticipated adverse device effects that may occur.

ANTICIPATED ADE	FREQUENCY
Urinary tract infection	Improbable
Irritation or minor pain in urethra	Improbable
Minor harm to urethra	Improbable

Table 9: Anticipated adverse device effects and their likely frequency rates.

Frequency rates are based on complaint levels received on SpeediCath®Standard Male as well as the risk management file.

14.3. Device deficiency

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

Primary and secondary endpoints that are measured during this investigation will not be required to be reported as device deficiencies. Example of a device deficiency could be disconnection of catheter tube to connector.

[redacted]

14.4. Serious adverse events

14.4.1. Serious adverse event (SAE)

A serious adverse event is an adverse event that:

- Led to death.
- Led to a serious deterioration in the 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 inpatient hospitalisation or prolongation of existing hospitalisation, or
  4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or function.
- Led to foetal distress, foetal 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 serious adverse event reporting.

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

14.4.2. 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.

14.4.3. Anticipated serious adverse device effect (ASADE)

There are no anticipated serious adverse device effects.

14.4.4. 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.

14.4.5. 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.

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 Practitioner 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.

[redacted]

14.5. Reporting and timelines

14.5.1. Investigator's reporting responsibilities

- PI must assess all (S)AE's that occur at his site.
- All serious adverse events and serious adverse device effects must be reported to the sponsor immediately, but no later than 3 calendar days after investigational site study personnel's awareness of the event.
- A device deficiency that could have led to a serious adverse event but did not do so because suitable action was taken, intervention had been made or because of fortunate circumstances should be reported to the sponsor immediately, but no later than 3 calendar days after investigational site study personnel's awareness of the event.
- New findings and/or updates in relation to already reported serious adverse events should also be reported to the sponsor within 3 calendar days after investigator became aware.
- Device deficiencies and all adverse device effects must be reported to sponsor within 10 days.

Device deficiencies and all adverse device effects must be documented immediately and with no undue delay on the safety reporting forms in the CRF.

All the serious adverse events listed above must be reported using 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 Clinical Manager, [redacted]

14.5.2. Sponsor's reporting responsibilities

It is the responsibility of sponsor to ensure that the following are reported to the relevant 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.

Sponsor must inform all investigators in writing within ten days after the sponsor is made aware, if an AE or Device Deficiency led to corrective actions (e.g change of IFU).

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

[redacted]

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 Ethics Committee of the Capital Region of Denmark and the Danish Medicine Agency.

If monitoring or auditing of the clinical investigation identifies serious or repeated deviations at the participating investigation site, sponsor will suspend or terminate the investigation site. The sponsor or investigator will inform the EC and the Danish Medicine Agency 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 Principal Investigator must sign the final version of the clinical investigation report or an affidavit, indicating their agreement with the contents.

The clinical investigation report will be submitted to Ethics Committee of the Capital Region of Denmark and the Danish Medicine Agency.

17. Publication policy

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

The investigation will be registered on a public accessible database, www.ClinicalTrial.gov, 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 CIP 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.

18. Bibliography

Literature Review Report Ziegler Natta and PEG 2000, Doc ID VV-0115146.

Li Wan Po A, Petersen B. J Clin Pharm Ther. 2006 Apr;31(2):161-5. How high should total pain-relief score be to obviate the need for analgesic remedication in acute pain? Estimation using signal detection theory and individual-patient meta-analysis.

[redacted]