Clinical Investigation Plan

CP277

Exploratory study investigating urodynamic parameters during catheterisation

November 2017 – June 2018

Master

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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 – CP277 Veeva: Clinical Study Agreement - CP277 (VV-0190329)
2.0	[redacted]	Adding explanation on recruitment advertisement in paragraph 6.2.3
3.0	[redacted]	Clarification of Urodynamic examination, paragraph 6.1 table 1 and 2. Clarification of Bacteria level on catheter in the baseline data of SCI and BPH subjects, paragraph 6.1.2.

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SYNOPSIS OF THE CLINICAL INVESTIGATION

Objective

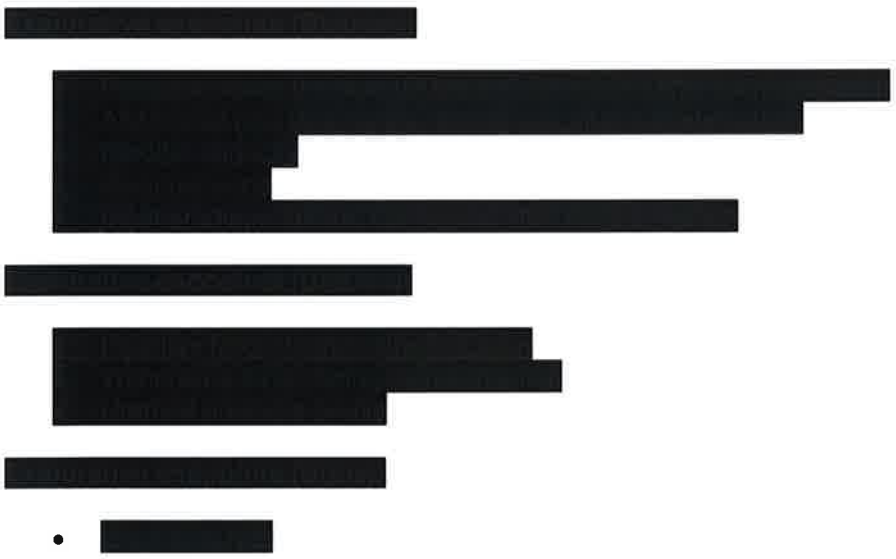
The aim of the study is to explore and understand how urodynamic parameters are affected when emptying the bladder with an intermittent catheter in healthy volunteers, patients with Spinal Cord Injury (SCI) and patients with enlarged prostate (BPH).

The primary objective is to investigate the urodynamic parameters in healthy volunteers emptying spontaneously and with an intermittent catheter (IC).

Secondary objective is to evaluate the urodynamic parameters in spinal cord injured patients as well as patients with enlarged prostate emptying their bladder with an intermittent catheter (IC).

Endpoints

Due to the explorative nature of the study, no primary endpoint is defined but endpoints are divided into three categories dependent on their relation to bladder, urethra or urine.



- [redacted]

Additionally

- Discomfort during catheter insertion and withdrawal on a Visual Analogue Scale
- Adverse events

Pass/fail criteria

The study will provide valuable insight into the development of pre-clinical models but no formal success criteria are applied in this exploratory study.

Design of the investigation

The investigation is conducted at one site and is an explorative study, estimated to last three months. The investigation is an open single arm investigation including 30 male subjects. 10 healthy volunteers, 10 patients with Spinal Cord Injury (SCI) and 10 patients with enlarged prostate (BPH).

The healthy volunteers included into the study will have three visits – an inclusion visit, a study visit including measurement of endpoints while spontaneous voiding of the bladder followed by a last visit measuring endpoints while emptying the bladder using a standard IC.

The subjects with SCI and BPH will have two visits. – the first visit includes a urine culture analysis and prophylactic antibiotic is prescribed per the result of the analysis. (Most IC users have bacteria in the urine and to

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decrease the risk of acquiring a urinary tract infection from the urodynamic examination, urine cultures are performed and prophylactic antibiotics will be prescribed per the result). The second visit is conducted while the patient is on antibiotic treatment and includes a urodynamic examination measuring all endpoints while emptying the bladder with a standard IC.

Population

The investigational population consists of healthy subjects, patients with SCI and patients with BPH who comply with the following inclusion and exclusion criteria:

Inclusion criteria

- Have given written informed consent and signed letter of authority
- Be at least 18 years of age and have full legal capacity
- Be a male

Healthy volunteers only,

- Have a negative urine multistix:
  - Leukocytes
  - Nitrite

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

- Willing to refrain from using analgesics up to 24 hours prior to catheterization visits

The two patient populations only,

- Use IC daily due to SCI or BPH and have used IC for at least 2 months

Exclusion criteria:

- Symptoms of urinary tract infections
- Have previously participated in this investigation
- Participate in other clinical investigations related urinary tract system during this investigation
- Known hypersensitivity toward any of the test products

Healthy volunteers only:

- Abnormalities, diseases or surgical procedures performed in the lower urinary tract (inclusion to termination).

Test products

The purpose of the investigation is to obtain urodynamic data while emptying the bladder [redacted] and therefore, no investigational devices are being investigated.

Investigation approval

Prior to commencing any activities related to the investigation, the Clinical Investigation Plan shall be approved by the Ethics Committee of the Capital Region of Denmark.

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LIST OF ABBREBIATIONS

ABBREVIATION	WRITTEN OUT	EXPLANATION
ADE	Adverse Device Effect	See section 13.1
AE	Adverse Event	See section 13.1
ASADE	Anticipated Serious Adverse Device Effect	See section 14.3.3
CIP	Clinical Investigation Plan	Describes the clinical investigation design and procedures
CRF	Case Report Form	Questionnaire to be used for data collection
CM	Clinical Manager	Qualified person overseeing the investigation is carried out in compliance with the investigation plan
DQF	Data Query Forms	A DQF is a query specifically used in clinical research. The DQF is the primary data query tool from the sponsor to clarify discrepancies and ask the investigator for clarification. The DQF is part of the data validation process in a clinical investigation.
EC	Ethics Committee	It is the responsibility of the committee system on health research ethics to ensure that from a research ethical point of view, health research projects are carried out in a responsible manner, and that the rights, safety and wellbeing of trial subjects participating in such biomedical research projects are protected
IFU	Instruction for Use	Manual describing the use of a medical device
ITT	Intention to Treat	
PI	Principal Investigator	Qualified person responsible for conducting the clinical investigation at an investigation site. If the clinical investigation is conducted by a team of individuals at an investigation site, the PI is the responsible leader of the team. Whether this is the responsibility of an individual or an institution can depend on national regulations.
PP	Per Protocol	
SADE	Serious Adverse Device Effect	See section 13.4
SAE	Serious Adverse Event	See section 13.4
USADE	Unanticipated Serious Adverse Device Effect	See section 13.4

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SIGNATURE PAGE

All Sponsor parties declare by their signature on the electronic signature page to follow the Clinical Investigation Plan CP277 in accordance with the Declaration of Helsinki, ISO 14155 and the Medical Device Directive.

SPONSOR

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SIGNATURE PAGE

Investigator hereby declare to follow the Clinical Investigation Plan CP277 in accordance with the Declaration of Helsinki, ISO 14155 and the Medical Device Directive.

PRINCIPAL INVESTIGATOR	***PRINCIPAL INVESTIGATOR***
[redacted]	*Signature*
	Date

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1. List of personnel involved in the Investigation

1.1. Sponsor representatives

CLINICAL MANAGER	STATISTICIAN
[redacted]	[redacted]
R&D SCIENTIST, PRE-CLINIC	**R&D SCIENTIST, PRE-CLINIC**
[redacted]	[redacted]
Scientific Manager	**Head of Clinical Operations**
[redacted]	[redacted]
Data Manager	
[redacted]	

In case of emergency, please contact the Clinical Manager (CM) from the above list of sponsor representatives.

1.2. Investigators

One site is included in the investigation

SITE 1 - PRINCIPAL INVESTIGATOR
[redacted]

1.3. Other

All delegated investigation 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 purpose of the investigation is to obtain urodynamic data while emptying the bladder [redacted] and therefore, no investigational devices are being investigated.

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 (1). Coloplast manufactures intermittent catheters and works continuously to improve them. During the development of new intermittent catheters, lab models are used to screen new catheter prototypes.

The data from the investigation will be compared to lab data [redacted]

4. Investigational device and clinical investigation risks and benefits

Risks associated with the investigation may be discomfort or stinging in the urethra during the urodynamic examination and the catheterisation. Furthermore, there may be a risk of micro trauma and haematuria after catheterisation, which heals within 1-3 days. After a urodynamic examination, there may be a risk of obtaining a urinary tract infection.

4.1. Anticipated clinical benefits

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

By participating in this investigation, the subjects will contribute with important data for developing novel lab models that can simulate bladder emptying and be used to develop improved intermittent catheters.

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 it may in the future benefit individuals who are dependent on intermittent catheters for emptying their bladder.

4.2. Possible interactions with concomitant medical treatments.

There is no known interaction between the planned study procedures and concomitant medication.

5. Objectives and hypotheses of the clinical investigation

5.1. Objective

The aim of the study is to explore and understand how urodynamic parameters are affected when emptying the bladder with an intermittent catheter in healthy volunteers, patients with Spinal Cord Injury (SCI) and patients with enlarged prostate (BPH).

The primary objective is to investigate the urodynamic parameters in healthy volunteers emptying spontaneously and with an intermittent catheter (IC).

Secondary objective is to evaluate the urodynamic parameters in spinal cord injured patients as well as patients with enlarged prostate emptying their bladder with an intermittent catheter (IC).

6. Design of the clinical investigation

6.1. General

The investigation is an explorative open single arm investigation including 30 male subjects. 10 healthy volunteers, 10 patients with SCI and 10 patients with BPH.

The healthy volunteers included into the study will have an information visit and three study visits – an inclusion visit (visit 0), a visit 1 measuring endpoints while spontaneous voiding of the bladder (0-7 days after visit 0) followed by a visit 2 measuring endpoints while emptying the bladder using a standard IC (4-15 days after visit 1). (Visit 0 and visit 1 can be the same day).

The subjects with SCI and enlarged prostate will have an information visit and two study visits. – an inclusion visit (visit 0) where a urine culture is analysed and prophylactic antibiotic is prescribed per the result of the analysis. (Most IC users have bacteria in the urine and to decrease the risk of acquiring a urinary tract infection from the urodynamic examination, urine cultures are performed and prophylactic antibiotics will be prescribed per the result). The second visit (visit 1) is conducted while the patient is on antibiotic treatment measuring all endpoints while emptying the bladder with a standard IC (4-15 days after visit 0 while subject is on prophylaxis antibiotics).

The investigation is conducted at one site and is an explorative study, estimated to last eight (8) months.

Table 1 and 2 illustrates the study period and the adherent study activities performed at each visit for the healthy volunteers, the SCI and BPI patients respectively.

Visit	Process	Activity
-	Study Information	• Subject Information
0	Inclusion	• Informed Consent Form • In- and exclusion criteria fulfilled • Urine multistix performed (leukocytes, nitrite and erythrocytes) • Baseline data collected and entered in the CRF by nurse • Relevant concomitant medication recorded • Schedule visit 1 (may be same day as visit 0)
1	Endpoints measured during normal voiding	• Check for use of analgesics and symptoms of UTI (and urine multistix performed if visit 1 is not the same day as visit 0) [redacted] • Standard Urodynamic examination performed (twice, first measuring is for adjustment and second measurement is recorded) • Registration of any adverse events and relevant concomitant medication • Schedule visit 2
2	End points measured during bladder emptying with IC	• Check for use of analgesics and symptoms of UTI (and urine multistix performed) • Special Urodynamic examination including flowrate performed (one measurement). Catheters to be used is one standard and one RIK catheter • One hour break [redacted]

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	[redacted] • Discomfort registered by subject on a Visual Analogue Scale • Registration of any adverse events and relevant concomitant medication • Termination form

Table 1 Study period including three (3) visits, Healthy volunteers

Visit	Process	Activity
-	Study Information	• Subject information
0	Inclusion	• Informed Consent Form • In- and exclusion criteria fulfilled • Baseline data collected and entered in the CRF by nurse • Relevant concomitant medication recorded • Urine multistix recorded, urine culture performed and antibiotic prescribed per bacteria present • Schedule visit 1 (during treatment with antibiotic) 5-14 days after visit 0
1	Catheterisation with test product 1	• Check for symptoms of UTI (and urine multistix performed) [redacted] • Special Urodynamic examination including flowrate performed (one measurement). Catheters to be used is one standard and one RIK catheter (for SCI pts an extension tube shall be used). • One hour break [redacted] • Discomfort registered by subject (if possible) on a Visual Analogue Scale • Registration of any adverse events and relevant concomitant medication • Termination form

Table 2 Study period including two (2) visits, SCI and BPH patients

6.1.1. Endpoints

Due to the explorative nature of the investigation, no primary endpoint is defined but endpoints are divided into three categories dependent on their relation to bladder, urethra or urine.

The statistical analysis to be performed on the explorative endpoints is described in Section 7.

[redacted]

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[redacted]

Discomfort measured during:

- Catheter insertion measured by subjects on a Visual Analogue Scale, VAS scale: 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

- Catheter withdrawal measured by subjects on a Visual Analogue Scale, VAS scale: 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

Safety data

- Adverse events

6.1.2. Baseline / Demographic data

The following baseline data is collected:

- Age
- Collection of urine samples for analysis for:
  - pH
  - Protein
  - Viscosity
  - Osmolality
  - Bacteria level
- Bladder wall condition (normal thickness, increased thickness, other, unknown)

For SCI and BPH pts:

- Reason for using IC
- Bacteria level on IC catheter used for collecting urine sample (using subject own catheter)
- Time using IC
- Number of catheterisations a day
- Brand name of catheter
- Possible to void spontaneously

6.1.3. Rationale for selection and measurement of endpoints

Intermittent catheterisation is the preferred method of bladder emptying for persons with spinal cord injuries and neurogenic bladder dysfunction. Coloplast manufactures intermittent catheters and works continuously to improve them. During the development of new intermittent catheters, lab models are used to screen new catheter prototypes.

[redacted]

6.1.4. Discussion of clinical investigation design

As no investigational product is investigated and the investigation is of explorative nature, the design is an open single arm investigation.

During the investigation, there must be 4-15 days between each study visit. The minimum period is set to allow potential micro trauma from study procedures to heal. The maximum period is set to meet logistical requirements in planning subjects' visits.

To explore and understand how urodynamic parameters are affected when emptying the bladder with an intermittent catheter in healthy volunteers, patients with SCI and patients with BPH, male subjects are chosen [redacted]
Many IC users have bacteria in the urine and to decrease the risk of acquiring a urinary tract infection from the urodynamic examination, urine cultures are performed and prophylactic antibiotics will be prescribed per the result.

6.2. Subjects

To be included in the investigation, the subjects must comply with the selection criteria described in section 6.2.1 and 7.

6.2.1. Inclusion criteria for subject selection

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

1. Have given written informed consent
2. Be at least 18 years of age and have full legal capacity
3. Me male
4. For healthy volunteers: Willing to comply with not using analgesics up to 24 hours prior to study visit
5. For healthy volunteers: Negative urine multistix (leukocytes and nitrite), or if positive, subsequent negative for bacterial growth in urine culture
6. For SCI and BPH patients: Use intermittent catheter daily and have used intermittent catheters for at least 2 months

Justification for inclusion criteria

1. To meet the Helsinki declaration
2. To meet the Helsinki declaration
3. To ensure data can be used to resembling the lab models with are using male pig urethras
4. Pain relief can affect endpoint related to discomfort.
5. To ensure the subject does not have a urinary tract infection at inclusion
6. To ensure data can be used to resembling the lab models
7. To ensure data can be used to resembling the lab

6.2.2. Exclusion criteria for subject selection

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

1. Symptoms of urinary tract infections (frequent urination, stinging and pain at urination)
2. Participate in other clinical investigations related to urinary tract system during this investigation (Inclusion → termination)

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3. For healthy volunteers: Abnormalities, diseases or surgical procedures performed in the lower urinary tract

Justification for exclusion criteria

1. To ensure that the subjects do not have urinary tract infection at inclusion. None of the symptoms may be present.

2. Other investigation guidelines/procedures may interfere with these investigational endpoints.

3. To ensure homogeneous group of urinary tracts where abnormalities, diseases or surgical procedures do not have an influence on measured parameters.

6.2.3. Recruitment and enrolment

Recruitment of potential subjects will begin once approvals have been obtained from the Ethics Committee of the Capital Region Denmark.
Recruitment will take place using subject records from the site as well as from Coloplast own subject database [redacted], www.forsøgsperson.dk and, if necessary, through advertisements in local newspapers.
Only users of intermittent catheter are registered in the Coloplast database, which after their initial registration have given oral consent to receive material about clinical investigations from Coloplast will be approached.

- Potential subjects are identified by the following search criteria in the Coloplast database: Be at least 18 years of age and have full legal capacity
- Be male
- Use intermittent catheter daily due to spinal cord injury or enlarged prostate
- Used IC for a period of at least 2 months

The identified potential subjects from the Coloplast User Database will receive by mail or email, the Subject Invitation Letter with the written subject information and "Forsøgspersoners rettigheder i et sundhedsvidenskabeligt forskningsprojekt" attached. If the subject is interested in participating, he is encouraged to contact the site and an information meeting is arranged.

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 an Invitation Letter with the written subject information and "Forsøgspersoners rettigheder i et sundhedsvidenskabeligt forskningsprojekt" attached. If the subject is interested in participating, he is encouraged to contact the site and an information meeting is arranged.

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. Interested potential subjects contact the Clinical Manager at Coloplast or a representative hereof. In- and exclusion criteria are 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 investigator or study nurse, who will contact the potential subject. If he still wishes to participate, an information meeting is arranged.
Potential subjects recruited in one of the above ways will, at visit 0, go through the informed consent process. Once enrolled in the study, the subject may then continue to in- and exclusion.

The informed consent process is described in Section 12.

6.2.4. 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:

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

Withdrawn subjects will not be replaced by new subjects.

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.

6.2.5. 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.

6.2.6. Total expected duration of the clinical investigation

The dates below are approximate and no subjects will be enrolled before the required approval from Ethics Committee of the Capital Region Denmark have been obtained. Changes greater than ± 2 months will be notified to EC.

Activity	Estimated time
First subject enrolled	November 2017
Last subject enrolled	May 2018
Last subject completed	June 2018
Final Report	June 2019

Table 3 Estimated timeline of the investigation

The investigation is terminated when the last subject has ended his participation. The same committee and authority will be informed of investigation termination within 90 days hereof (unless the investigation is terminated prematurely where information is given 15 days after termination, including the reason for premature termination).

6.2.7. Total number of subjects

During the investigation period, there will be enrolled 30 subjects. A subject is considered enrolled in the investigation when he has signed and dated the Informed Consent Form.

6.3. Procedures

6.3.1. Clinical investigation-related procedures

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

Study period

Healthy Volunteers:
During the study period, each subject of the healthy volunteers has an information visit and three (3) study visits: Visits 0, 1 and 2. Visit 0 and visit 1 can be the same day.

Information Visit:
Subject will be given information about the investigation by the investigator and have a minimum of 24 hours before deciding on participating in the investigation.

Visit 0 (Inclusion):
Subject will sign the Informed Consent Form (see section 12). It is then ensured that in- and exclusion criteria are met, including urine analysis with multistix, leukocytes and nitrite (Multistix 7, Siemens). Enrolled subjects are allocated a subject number, and hereafter demographics, baseline data and concomitant medication is recorded. A urine sample is collected for baseline data analysis performed by Coloplast laboratory.

Visit 1, 0-7 days after last visit (Normal Voiding):
Subject is asked about symptoms for urinary tract infections (frequent urination, stinging or pain at urination) and a urine analysis with multistix, leukocytes and nitrite (Multistix 7, Siemens) is performed. The subject is asked about use of analgesics up to 24 hours prior to the visit and if the multistix analysis is showing negative in leukocytes and nitrite and there are no symptoms of urinary tract infection and no use of analgesics, the subject will continue with the standard urodynamic examinations (measured twice, first measuring is for adjustment and second measurement is recorded), [redacted].

The nurse register relevant data in the CRF, including possible adverse events and relevant concomitant medication. Next visit is scheduled.

Visit 2, 4-15 after last visit (IC)
Subject is asked about symptoms for urinary tract infections (frequent urination, stinging or pain at urination) and a urine analysis with multistix, leukocytes and nitrite (Multistix 7, Siemens) is performed. The subject is asked about use of analgesics up to 24 hours prior to the visit and if the multistix analysis is showing negative in leukocytes and nitrite and there are no symptoms of urinary tract infection and no use of analgesics, the subject will continue with the special urodynamic examination [redacted]
In addition, the subject evaluates the discomfort of the insertion and withdrawal of the intermittent catheter using a VAS scale.

The nurse register the subject evaluation and other relevant data in the CRF, including possible adverse events and relevant concomitant medication.

[redacted]

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The subject has completed the investigation and the termination form is completed.

SCI and BPH patients:
During the study period, each subject of the SCI and BPH population has an information visit and two (2) study visits: Visits 0 and 1.

Information Visit:
Subject will be given information about the investigation by the investigator and have a minimum of 24 hours before deciding on participating in the investigation.

Visit 0 (Inclusion):
Subject will sign the Informed Consent Form (see section 12). It is then ensured that in- and exclusion criteria are met, including urine analysis with multistix, leukocytes and nitrite (Multistix 7, Siemens). Enrolled subjects are allocated a subject number, and hereafter demographics, baseline data and concomitant medication is recorded. A urine culture is performed and antibiotics is prescribed per bacteria present and a urine sample is collected for baseline data analysis performed by Coloplast laboratory. Next visit is scheduled.

Visit 1, 4-15 days after visit 0 (IC):
Subject must be on prescribed prophylaxis antibiotic and is asked about symptoms for urinary tract infections (frequent urination, stinging or pain at urination). A urine analysis with multistix, leukocytes and nitrite (Multistix 7, Siemens) is performed and if there are no symptoms of urinary tract infection, the subject will continue with the special urodynamic examination [redacted].

In addition, the subject evaluates the discomfort of the insertion and withdrawal of the intermittent catheter using a VAS scale.

The nurse register the subject evaluation and other relevant data in the CRF, including possible adverse events and relevant concomitant medication.

[redacted]

The subject has completed the investigation and the termination form is completed.

6.3.2. 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 complete the CRF and how to report possible safety issues to Sponsor. All training will be documented by site and sponsor signing a Training Log
- Analysis of collected Baseline Urine samples
- Bacterial analysis of collected used catheters
- Support during the recruitment process
- Monitoring

No biobank is established. All urine samples in the clinical investigation (baseline data) will be destructed immediately after laboratory analysis.

6.3.3. Foreseeable factors that may compromise the outcome / results

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

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6.3.4. Flow-chart

The scheduled visits and corresponding assessments for the period of the investigation is shown I table 4 and 5.

ACTIVITY	INFOR-MATION VISIT	VISIT 0 (INCLU-SION)	VISIT 1 (NORMAL VOIDING)	VISIT 2 (IC)
Subject Oral and written information	X			
Written informed consent		X		
Check of inclusion and exclusion criteria, including urine analysis		X		
Allocation of Subject number		X		
Demographic and Baseline data		X		
Urine sample for measuring baseline parameters		X		
Question subject about use of analgesics 24 hours prior to visit			X	X
Question subject about symptoms of UTI		X	X	X
Urine multistix performed		X	X	X
[redacted]			X	X
[redacted]			X	
Standard Urodynamic examination performed [redacted]			X	
Special Urodynamic examination performed [redacted]				X
[redacted]				X
[redacted]				X
Subject registration of discomfort using a Visual Analogue Scale (VAS).				X
Relevant concomitant medication		X	X	X
AEs/SAEs			X	X
Termination form				X

Table 4 chart showing the connection between visits and assessments for Healthy volunteers.

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ACTIVITY	INFORMATION VISIT	VISIT 0 (INCLUSION)	VISIT 1 (IC)
Subject Oral and written information	X		
Written informed consent		X	
Check of inclusion and exclusion criteria, including urine analysis		X	
Allocation of Subject number		X	
Demographic and Baseline data		X	
Urine sample for measuring baseline parameters		X	
Question subject about symptoms of UTI		X	X
Urine multistix performed		X	X
Urine culture performed and antibiotic prescribed per bacteria present		X	
[redacted]			X
[redacted]			X
Special Urodynamic examination [redacted]			X
[redacted]			X
[redacted]			X
[redacted]			X
Subject registration of discomfort using a Visual Analogue Scale (VAS).			X
Relevant concomitant medication		X	X
AEs/SAEs			X
Termination form			X

Table 5 chart showing the connection between visits and assessments for SCI and BPH patients.

6.3.5. Case Report Forms

All assessments and observations throughout the investigation for each subject must be carefully recorded in the CRF.

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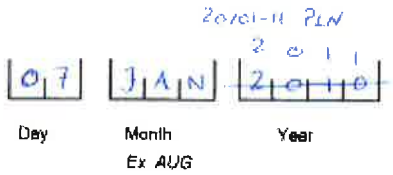
The CRFs are printed and supplied by sponsor. The CRFs are printed on NCR paper to have one copy for investigator and one copy for sponsor (original copy). A CRF is provided for each subject. It is the responsibility of the Investigator that all data are entered promptly and correctly.

Each CRF has an identification number and a printed instruction for completion.

The sponsor will be responsible for training the investigator and the study nurse in completion of the CRF. The nurse 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.
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:

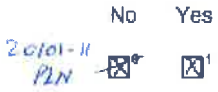


Figure 1 Two examples of how to make corrections in the CRF

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 sponsor representative(s) will send the CRFs to Coloplast A/S on an ongoing basis after each site visit or as soon as possible after a subject has terminated their last visit.

6.3.6. Concomitant treatment

Healthy subjects may not use analgesics 24 hours prior to catheterisation visits, see inclusion criteria Section 6.2.1

Subjects may not participate in other clinical investigations related to urinary tract system during this investigation, see exclusion criteria Section 6.2.2

Most IC users have bacteria in the urine and to decrease the risk of acquiring a urinary tract infection from the urodynamic examination, urine cultures are performed and prophylactic antibiotics will be prescribed per the result.

6.3.7. Supplementary materials and equipment (if applicable)

Supplementing devices or instruments normally used for catheterisation (e.g. medical gloves, tray for urine collection) and for the urodynamic examinations are supplied by investigator.

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The intermittent catheters used in the investigation for measuring endpoints while emptying the bladder with an IC are SpeediCath catheters sponsored by Coloplast A/S. SpeediCath is a CE marked class I, standard sterile catheters intended for intermittent catheterisation of the bladder through the urethra.

6.4. 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 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 15 subjects

Monitoring visit three (3) will be conducted as soon as possible after the completion of the last 15 subjects

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 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 [redacted]

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.

6.4.1. Source data verification

Investigation source data are: the CRFs, Informed Consent Forms, Urodynamic Graphs and tables.
In addition, data completed electronically in Excel-sheets which includes the following data [redacted], bacterial analysis and measured discomfort during catheterisation.

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" [redacted]

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

6.4.2. 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.

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7. Statistical considerations

7.1. Statistical design, method and analytical procedures

All statistical analyses described in the protocol are made with SAS version 9.4 (SAS Institute Inc., Cary, NC). Further exploratory analysis might be performed with other software.

Definition of analysis populations

The ITT population (full analysis set) will be constituted by all included subjects who:

- Have provided valid informed consent
- Have valid information for at least one of the endpoints

Invalid individual data points may be omitted from analysis even though the corresponding subject is part of the ITT population. Any exclusion of data points will be documented.

The Safety population (basis for presentation of AEs) will constitute by subjects who have given informed consent.

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

Analysis of the explorative endpoint

Baseline data will be summarized and listed by type of subject group (spinal cord injury, subjects with enlarged prostate and healthy volunteers) and in total.

For each visit, explorative endpoints will be summarized and listed by type of subject group (spinal cord injury, subjects with enlarged prostate and healthy volunteers) and in total. If the endpoint is a curve ([redacted] only relevant characteristics of the curve (e.g. peak of the curve) will be summarised and listed.

[redacted]

If relevant, explorative statistical analyses can be performed.

Adverse events will be listed based on the safety population.

7.2. Sample size

As this is an exploratory study no formal sample size calculation has been performed. It is assumed that 10 subjects with spinal cord injury, 10 subjects with enlarged prostate and 10 healthy volunteers will be adequate for the characterization.

7.3. Level of significance and power

If explorative statistical analyses are performed a significance level of 5% will be applied.

7.4. Drop-out

Due to the exploratory nature of the study, drop-out subjects will not be replaced.

7.5. Pass/fail criteria

No formal pass/fail criteria are applied in this explorative pilot evaluation.

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7.6. Interim analysis

No interim analysis will be performed.

7.7. Statistical reason for termination of investigation

There is 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 report.

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8. Data management

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

Data management and statistical analyses is carried out by the 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 CM if this period should be longer for their sites per local regulation.

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9. Amendments to the CIP

Any significant changes to the CIP are:

- Agreed between sponsor and Principal Investigator(PI).
- 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 and approved by the EC before implementation.

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

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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 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.

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11. 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, 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".
- Any applicable regional or national regulations will be specified in the country specific CIP.

11.1. Ethics committee and regulatory authorities

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

Sponsor will notify the EC concerned of the end of the clinical investigation.

11.2. 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.

11.3. Indemnity

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

[redacted]

11.4. 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

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contract. Investigator fee, including subject remuneration, is estimated up to [redacted]. Investigator has no apparent conflict of interest.

Subjects will be remunerated with a voucher equal to [redacted] per completed visit equal to two (2) vouchers per subject upon completion of the investigation. This is to compensate for any inconvenience caused during the catheterisations, time used and travel expenses.

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12. 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 written form. CM is responsible for writing the information and providing it to investigators that will further provide it to the subjects. If applicable, all affected subjects shall be asked to confirm their continuing informed consent in writing.

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

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13. Adverse events, serious adverse events and device deficiencies

13.1. Adverse events

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

13.2. Adverse device effect

An adverse event, which is related to the use of the 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.

Although not testing a medical device in this investigation, several procedures include use of CE-marked medical devices (e.g. catheters for urodynamic examinations).

ANTICIPATED ADE RELATED TO URODYNAMIC PROCEDURES	INCIDENCE RATE SCI/BPH PTS	INCIDENCE RATE HEALTHY VOLUNTEERS
Urinary tract infection	Unlikely	Very unlikely
Macroscopic haematuria	Unlikely	Unlikely
Stinging and pain in urethra during examination	Likely	Likely

Table 6 Anticipated adverse device effects and their likely incidence rates.
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%).

13.3. Device deficiency

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

13.4. Serious adverse events

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.

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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.

13.4.1. 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.

13.4.2. Anticipated serious adverse device effect

There are no anticipated serious adverse device effects.

13.4.3. 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.

13.5. 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.

13.6. Reporting and timelines

13.6.1. Investigators 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 sponsor immediately but no later than 3 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 immediately but no later than 3 calendar days.
- New findings and/or updates in relation to already reported serious events should also be reported to sponsor within 3 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: [redacted]

In cases where a mail is not reachable, please call Clinical Manager, [redacted].

13.6.2. 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 7 calendar days following the date of awareness by sponsor.

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- 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.

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14. 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 Ethics Committee of the Capital Region of Denmark.

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 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.

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15. 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.

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16. Publication policy

16.1. General

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.

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17. Bibliography

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