# Clinical Investigation Plan

## CP304

## Exploratory investigation of data obtained from a sensor connected to an intermittent catheter

March 2019 – August 2019

Master

## CHANGE LOG

| VERSION NUMBER | ISSUED BY *(INITIALS)* | COMMENTS (MAJOR CHANGES SINCE LAST REVISION) |
|---|---|---|
| 1.0 | [redacted] | Document established in template version 5.0 |
| 2.0 | [redacted] | p12: Label added |
| 3.0 | [redacted] | Minor editorial changes<br>p12: Label changed to label specifying "Single use"<br>p18: Subjects are requested to meet with full bladder at visit 1 added<br>p21: Concomitant disease deleted<br>p24+25: remuneration with raised from DKK1000 to DKK 1200<br>p26: Confidentiality Agreement changed to Secrecy Agreement<br>p26 consent to pass on social security number (CPR-number) to the Danish tax authorities, added |
| 4.0 | [redacted] | p22: As this study only consist of one study visit, expected drop-outs are 0. Should there be a drop-out, will these be replaced until 12 patients has finalised visit 1.<br>p26: Deleted: This procedure also applies to informed consent obtained from a subject's legal representative. The procedure cannot waive the subjects' legal rights. |
| 5.0 | [redacted] | p7+p15: Primary endpoint: "Sensor capability to generate a readable sensor profile" added. Exploratory Secondary endpoints deleted<br>p12: Label with expiry date pictogram added<br><br>p15 6.1.3: "Due to the early concept supporting purpose of this trial, no primary endpoint is defined" deleted.<br><br>p18: Termination section added.<br><br>P19: Tabel 1 "Written informed consent" changed to "Signed informed consent". Signed Letter of authority, "Investigator" replaced by "Subject"<br><br>"...and endpoints – during catheterization" deleted<br><br>"Urine pressure prior to and during voiding (sensor)" Changed to "Sensor data prior to and during voiding"<br><br>p20" 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". Changed to<br>"Signed informed consent, signed Letter of authority, in- and exclusion criteria and all Adverse events occurring in the investigation will be 100% monitored for all subjects enrolled in the investigation.<br><br>p22: "Readable sensor profiles versus non-readable sensor profiles will be summarized" added. "Analysis of explorative secondary endpoints" changed to "Analysis of primary endpoint".<br><br>p23: Clinical Investigation Plan deviations, section 10 updated. |
| 6.0 | [redacted] | The overall timeline for the study has been changed from December 2018- March 2019, till March 2019- August 2019. |

| | | |
|---|---|---|
| | | P12:<br>Medical Affairs Project Manager changed<br>Clinical Manager changed<br>Head of Clinical Manager changed<br>Medical Director deleted<br><br>P17:<br>Amendment submission date added<br>First Patient First Visit: updated<br>Last Patient Last Visit: updated<br>Report date: updated |

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## > SYNOPSIS OF THE CLINICAL INVESTIGATION

### Background

Intermittent catheterisation is the preferred method of bladder emptying for persons with chronic urine retention due to neurogenic bladder dysfunction following e.g. spinal cord injury, or due to an enlarged prostate, etc. Coloplast A/S manufactures different catheters and devices for incontinence and works continuously to improve them.

The purpose of this study is to test the pressure sensor capabilities in a clinical environment. The sensor has shown good readable results in pre-clinical tests. Given the complex pressure conditions in the human body with pressure contributions from e.g. body movement, bowel peristalsis, heartbeat etc, the next step is to test the sensor capability to generate readable pressure measurement before and during catheterisation in healthy volunteers and to evaluate the extent of artifacts on the sensor readings.

[redacted]

### Objective

To explore data obtained from a sensor connected to an intermittent catheter prior to and during voiding.

### Primary endpoint and secondary endpoint(s)

Primary endpoint

Sensor capability to generate a readable sensor profile

Secondary endpoints

Adverse events

### Pass/fail criteria

No formal success criteria are applied in this exploratory study. However, it is expected that the study will provide useful data to guide efforts in development of the pressure sensor.

### Design of the investigation

Single arm - open-label study.

Each participating subject will be asked to conduct:

- Information visit
- Visit 0 – inclusion visit
- Visit 1 – Test visit

### Population

The population consists of 12 healthy volunteers. Both male and female are eligible for enrolment. Minimum 4 subjects of each gender must be enrolled and subjects must comply with the following inclusion and exclusion criteria:

| Inclusion criteria: | Exclusion criteria: |
|---|---|
| 1. Have given written informed consent<br>2. Be at least 18 years of age and have full legal capacity<br>3. Negative pregnancy test for fertile women | 1. Previous history of significant genitourinary disease including congenital abnormalities and surgical procedures performed in the urinary tract<br>2. Symptoms of urinary tract infections (frequent urination, stinging and pain at urination)<br>3. Participation in any other clinical investigations during this investigation (Inclusion → termination)<br>4. Known hypersensitivity toward any of the test products<br>5. Are pregnant (positive pregnancy test) or breast feeding. |

### Test products

The tested medical device is a pressure sensor connected to an intermittent CE-marked commercially available catheter. The sensor is built around a tubular part that will be connected at the end of the catheter connector: urine will flow through the catheter directly into sensor lumen and out into toilet.

### Investigation approval

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

## > LIST OF ABBREBIATIONS

| ABBREVIATION | WRITTEN OUT | EXPLANATION |
|---|---|---|
| AE | Adverse Event | See section 14 |
| CA | Competent Authority. In this CIP the Danish Medicines Agency. | |
| CIP | Clinical Investigation Plan | |
| CM | Clinical Manager | Coloplast A/S study operational responsible and author of this Evaluation |
| CRF | Case Report Form | |
| 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 | |
| LSO | Last Subject Out | |
| 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. |
| SAE | Serious Adverse Event | |

## > SIGNATURE PAGE

All sponsor representatives declare by their signature on the electronic signature page that they will follow this Clinical Investigation Plan CP304 in accordance with the Declaration of Helsinki, ISO 14155 and the Medical Device Directive/Regulation.

**SPONSOR**

Coloplast A/S

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DK - 3050 Humlebæk

Denmark

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## > SIGNATURE PAGE

Principal Investigator hereby declare by his signature to follow this Clinical Investigation Plan CP304 in accordance with the Declaration of Helsinki, ISO 14155 and the Medical Device Directive/Regulation.

| PRINCIPAL INVESTIGATOR | PRINCIPAL INVESTIGATOR |
|---|---|
| [redacted] | Signature |
| | Date |

# 1. List of personnel involved in the Investigation

## 1.1. Investigator

| PRINCIPLE INVESTIGATOR (PI) |
| --- |
| [redacted] |

## 1.2. Sponsor representatives

| SENIOR STATISTICIAN | HEAD OF CLINICAL OPERATIONS |
| --- | --- |
| [redacted] | [redacted] |
| **MEDICAL AFFAIRS PROJECT MANAGER** | **SCIENTIFIC MANAGER** |
| [redacted] | [redacted] |
| **CLINICAL MANAGER** | |
| [redacted] | |

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

## 1.3. Other

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

# 2. Identification and description of the investigational device

## 2.1. Manufacture

Responsible for manufacturing the investigational device:

Coloplast A/S
Holtedam 1
3050 Humlebæk
Denmark.

### 2.1.1. Identification, traceability and labelling of device


### 2.1.2. Clinical investigation purpose of device

The purpose of the investigational device in the proposed clinical investigation is to capture pressure data prior to and during voiding using a CE-marked commercially available catheter.

### 2.1.3. Intended population for the device

People who are depending on intermittent catheterization will be eligible to use the final device when and if commercially available.

### 2.1.4. Description of investigational device

The medical device subject to test, is a sensor connected to an intermittent CE-marked commercially available catheter, as shown on the figure below. Catheters to be used will be SpeediCath® Standard male/female, Nelaton tip. The investigational device will not be in direct contact with subjects.

**Figure 1 Test device connected to catheter and data capture**

### 2.1.5. Handling and training

Site staff will receive proper training in the use of the device prior to study start.

## 3. Justification for the conduct of the clinical investigation

Intermittent catheterisation is the preferred method of bladder emptying for persons with chronic urine retention due to neurogenic bladder dysfunction following e.g. spinal cord injury, or due to an enlarged prostate, etc. Coloplast A/S manufactures different catheters and devices for incontinence and works continuously to improve them.

The purpose of this study is to test the pressure sensor capabilities in a clinical environment. The sensor has shown good readable results in pre-clinical tests. Given the complex pressure conditions in the human body with pressure contributions from e.g. body movement, bowel peristalsis, heartbeat etc, the next step is to test the sensor capability to generate readable pressure measurement before and during catheterisation in healthy volunteers and to evaluate the extent of artifacts on the sensor readings.

[redacted]

# 4. Ethical Considerations, risks and benefits

The evaluation is conducted in accordance with current law and applicable standards see section 12.

The rights, safety and well-being of human subjects will prevail over interest of science and society.

Subjects participating in the evaluation will be catheterized using a CE-marked commercially available catheter with the test device connected. The catheterization will be performed by urology nurses from Rigshospitalet Department of Urology with many years of experience in conducting intermittent catheterization.

There are no direct benefits for the participating subjects involved, but, by participating in this investigation, the subjects will contribute with important information for developing improved solutions for urinary intermittent catheterisation, that in turn may benefit individuals who are dependent on catheters for emptying their bladder.

The evaluation is conducted in accordance with 'The Declaration of Helsinki', 1964, last amended at the 64th WMA General Assembly, Fortaleza, October 2013, and ISO 14155 and the Medical Device Directive/Regulation.

# 5. Objectives and hypotheses of the clinical investigation

## 5.1. Objective

The objective is to explore data obtained from a sensor connected to an intermittent catheter prior to and during voiding.

## 5.2. Risks and anticipated adverse device effects to be assessed

Risks associated with the investigation may be discomfort or stinging in the urethra during the catheterisation. Furthermore, there may be a risk of micro-trauma and haematuria after catheterisation, which is expected to heal within 1-3 days. The trial setting is not expected to result in increased frequency or severity of the known risks associated with urethral catheterisation

# 6. Design of the clinical investigation

## 6.1. General

This clinical investigation is based on an open explorative design evaluating the sensor ability to record readable data in healthy volunteers and the extend of artifacts influencing data quality and readability in healthy volunteers.

**Overall:**

- Single arm. Open-labelled, not randomized
- Healthy volunteers

**Duration:**

Information visit:

Oral and written information about the evaluation is given by the PI or his/her representative. Subjects can continue to visit 0, inclusion visit, the same day - if the subject has decided on participation and practical possible.

Visit 0 – Inclusion visit:

Informed consent signed.

Subjects can continue to visit 1 - test visit the same day - if practical possible.

Visit 1 – test visit:

1h test visit at Rigshospitalet. Fertile females will be asked to perform a pregnancy test. Subject is asked about symptoms for urinary tract infections (frequent urination, stinging or pain at urination). If negative for these symptoms, the subject will be catheterised with (SpeediCath® Standard, male/female, Nelaton tip depending of the gender) with fitted pressure sensor. The urine is led into a standard urine flowmeter.

### 6.1.1. Primary endpoint

**Primary endpoint**
Sensor capability to generate a readable sensor profile.

### 6.1.2. Secondary end points and exploratory endpoints

**Secondary endpoints**

- Adverse events

### 6.1.3. Rationale for selection of measurements and endpoints

The endpoints have been chosen to explore pressure sensor capability to generate readable pressure data in a catheter in a clinical environment.

Data recordings will be considered versus what is known for urine parameters from physiology, clinical practice and will be considered versus background data obtained via a standard uroflowmeter during voiding.

### 6.1.4. Discussion of clinical investigation design

This is a single arm, open-labelled, not randomized investigation. The population consists of 12 healthy volunteers. Both male and female are eligible for enrolment. Minimum 4 subjects of each gender must be enrolled for one test visit. The reason for this design is the exploratory nature of the investigation.

## 6.2. Investigational device and comparator(s)

The evaluation does not include comparator devices.

## 6.3. Subjects

To be included in the investigation, the subjects must comply with the selection criteria described in section 6.3.1 .

### 6.3.1. Inclusion criteria for subject selection

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

**Inclusion criteria:**

1. Have given written informed consent
2. Be at least 18 years of age and have full legal capacity
3. Negative pregnancy test for fertile women

Inclusion 3: Women are considered fertile if they have had a least one period during the last 12 months

### 6.3.2. Exclusion criteria for subject selection

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

**Exclusion criteria:**

1. Previous history of significant genitourinary disease including congenital abnormalities and surgical procedures performed in the urinary tract
2. Symptoms of urinary tract infections (frequent urination, stinging and pain at urination)
3. Participation in any other clinical investigations during this investigation (Inclusion → termination)
4. Known hypersensitivity toward any of the test products
5. Are pregnant (positive pregnancy test) or breast feeding.

**Justification for exclusion criteria:**

1. Genitourinary abnormalities, diseases or surgical procedures may have an impact on the results of data and catheterization may be unnecessary uncomfortable for the subjects.
2. To ensure that the subjects do not have UTI at inclusion. In the event of UTI, catheterisation would be unnecessarily uncomfortable. None of the symptoms may be present.
3. To eliminate uncertainty whether any Adverse Events (AE's) or Serious Adverse Events (SAE's) occurring during the study relate to the use of the herein tested products, and to eliminate unintentional effect from other devices/medicines on this study's data.
4. Unnecessary harm for the subjects.
5. To eliminate the risk of UTI in pregnant or breastfeeding women.

### 6.3.3. Recruitment and enrolment

Recruitment of potential subjects will begin once approval have been obtained from the Ethics Committee of the Capital Region Denmark and the Danish Medicines Agency.

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, who have expressed interest in future clinical investigations). The identified potential subjects will receive written subject information and "Forsøgspersoners rettigheder i et sundhedsvidenskabeligt forskningsprojekt". If the subject is interested in participating, 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 and social medias. Interested potential subjects must contact the Clinical Manager at Coloplast A/S 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/she 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/she still wishes to participate, an information meeting is arranged.

The informed consent process is described in Section 13.

### 6.3.4. Subject withdrawal criteria

The subject can withdraw from the clinical investigation at any time for whatever reason without any consequences for their future treatment outside the investigation. The investigator may withdraw a subject from the investigation at any time if the investigator judge withdrawal to be in the subject's interest.

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

- Non-compliance with the Clinical Investigation Plan impacting the scientific integrity of the evaluation.
- If a subject's safety and well-being is compromised by further participation.

A subject who is withdrawn from the investigation, for any reason, will be encouraged to contact the investigator if problems arise that the subject believes are related to the investigation

### 6.3.5. Point of enrolment

A subject is considered enrolled in the investigation when the written informed consent is obtained.

### 6.3.6. Total expected duration of the clinical investigation

The dates below are approximate, and no subjects will be enrolled before all required approvals have been obtained.

- Submission to EC and CA: October 2018
- Amended submission: March 2019
- First patient in: March 2019
- Last patient out: August 2019
- Report: August 2020

### 6.3.7. Total number of subjects

12 healthy volunteers will be enrolled in this study. Both male and female are eligible for enrolment. No differences between male and female data are expected, but since the final device should comply with both male and female catheters, it is decided to include both male and female in the study.

Minimum 4 subjects of each gender must be enrolled. The reason for this to eliminate an outlaying data curve relation to gender.

## 6.4. Procedures

### 6.4.1. Clinical investigation-related procedures

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

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

**Visit 0 - Inclusion - approx. 30 min**

Information:

If a potential subject is interested in participating, an information visit will be arranged in a room reserved to ensure privacy and quiet surroundings at the site.

When arranging the visit, it will be ensured, that the subject has received the Subject Information Form prior to the visit and the subjects will receive both written and verbal information about the possibility of bringing a companion to the informational visit and to any possible subsequent visits. During the information visit, the Investigator or delegated personnel, will provide oral information about the investigation based on the Subject Information Form. The subjects have the right to wait 24h before deciding on participation. The information visit and the Visit 0 can be the same day.

Informed consent:

If/when the subject decides to participate he will be asked to sign the Informed Consent Signature Form and other relevant forms (see section 13). If a subject so desires, and it is certain that it is understood what the investigation entails and the relevant forms have been signed, it is then ensured that in- and exclusion criteria are met. Enrolled subjects are allocated a subject number, baseline data and concomitant medications is recorded by Investigator or delegated personnel.

Visit 0 and Test Visit 1 can be combined.

**Visit 1 – Test – approximately one hour**

Subjects are requested to meet for this visit with a fairly full bladder (avoided urination within 2 hours prior to the visit) or they will be offered a large glass of water and wait for this to reach the bladder. Fertile females will be asked to perform a pregnancy test. Subjects are asked about symptoms for urinary tract infections (frequent urination, stinging or pain at urination). If negative for these symptoms, the subject will be catheterised with SpeediCath® Standard, male/female, Nelaton tip depending of the gender after the sensor has been connected onto the catheter. The bladder will be emptied via a catheter into a standard urine flowmeter, measuring urine flow, by a nurse.

**Termination – end of visit 1**

Subjects who leave the study will continue to "Termination", at which the PI or a person delegated by the PI will complete the Termination form. The study is completed by completion of visit 1 and the Termination form will be completed by the end of visit 1 at the latest. Except from the Medical care of subjects described in section 14.5, no follow up or data capture will be conducted after the subject has left the study.

### 6.4.2. Activities performed by sponsor representatives

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

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

### 6.4.3. Foreseeable factors that may compromise the outcome / results

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

### 6.4.4. Flow-chart

| General | PERFORMED BY | SOURCE | INFORMATION AND INCLUSION VISIT 0 | VISIT 1 | TERMINATION END OF VISIT 1 |
|---|---|---|---|---|---|
| Oral information | Investigator | NA | X | | |
| Signed informed consent | Subject | Informed consent form | X | | |
| Signed Letter of authority | Subject | Letter of Authority Form | X | | |
| Signed secrecy agreement | Subject | Secrecy form | X | | |
| Concomitant medication registered | Investigator | CRF | X | | |
| Check of in- and exclusion criteria | Investigator | CRF | X | | |
| Allocation to subject number and sensor serial number | Investigator | CRF | X | | |
| Insurance of subjects well-being and compliance with CIP | Investigator | CRF | X | X | X |
| **Registration of Baseline data** | | | | | |
| Date of birth | Investigator | CRF | | X | |
| Gender | Investigator | CRF | | X | |
| **Check for symptoms of UTI before catheterisation** | | | | | |
| Check for symptoms of UTI (frequent urination, stinging and pain at urination) | Investigator | CRF | | X | |
| Catheterisation | Investigator | CRF | | X | |
| **Registration of measurements** | | | | | |
| Sensor data prior to and during voiding. | Investigator | Data points | | X | |
| Urine flow profile (uroflowmeter)<br>- Max flow rate (mL/s)<br>- Middle flow rate (mL/s)<br>- Voiding time (s)<br>- Flow time (s)<br>- Time to max flow (s)<br>- Voided volume (mL) | Investigator | Printed graph | | X | |
| AEs/ADEs/SAEs/SADEs | Investigator | CRF | | X | X |
| **Registration of termination** | | | | | |
| Termination form. Completed | Investigator | CRF | | | X |

**Table 1 chart showing the connection between visits and assessments**

### 6.4.5. Case Report Forms

The CRFs are printed and supplied by sponsor and one 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.

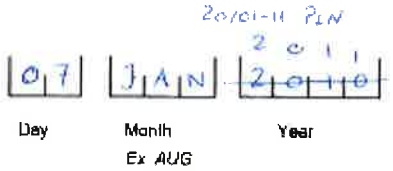
The sponsor will be responsible for training the investigator and the study nurse in completion of the CRF.

The CRF will clearly state which parts are to be completed by whom.

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:**

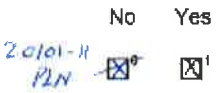



**Figure 2 Two examples of how to make corrections in the CRF**

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.

### 6.4.6. Supplementary materials and equipment

Supplementing devices or instruments normally used for catheterisation (e.g. medical gloves, tray for urine collection), uroflow meter and CE-marked commercial available catheters SpeediCath® Standard, male/female, Nelaton tip.

## 6.5. 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 will be completed as soon as possible after the last subject has completed the investigation
- Monitoring visit three, Close out visit, will be conducted as soon as possible after LSO

Signed informed consent, signed Letter of authority, in- and exclusion criteria and all Adverse events occurring in the investigation will be 100% monitored for all subjects enrolled in the investigation.
Investigation Site File shall be monitored for 100% completion per the Investigation File Requirement Checklist.

Monitoring activities conducted by the clinical manager will be documented in the site visit report applicable to the conducted visit. A summary describing the observation(s) and actions required shall be provided as soon as reasonably possible to the investigator after the conducted monitoring visit. The sponsor representative will have close contact to the site in the recruitment period to ensure that any concerns, problems or recruitment challenges are solved with the site in a timely manner.

### 6.5.1. Source data verification

Source data verification will be performed to the extent it is possible.

The Source Data Specification Form must be completed at the initiation visit detailing the location of the source data for each data point.

For each catherisation, pressure and flow measurements will be graphically presented over time and the data quality visually evaluated and will be filed on a secure data drive

Data points for data verification:

- Informed Consent Forms
- Letter of Authority
- In- / Exclusion criteria
- Concomitant medication
- AE/ADE
- other

The informed consent forms must be 100% verified for timely completeness.

The Letter of Authority form must also be 100% verified for timely completeness.

Only the investigator, delegated site personnel and the sponsor representatives will have access to all the CRFs. The subject will have access to his/her own CRF.

### 6.5.2. 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 A/S internal quality audit plan and procedures.

## 7. Statistical considerations

### 7.1. Statistical design, method and analytical procedures

Data will be presented using SAS version 9.4 (SAS Institute Inc., Cary, NC).

Exploratory qualitative analysis will be performed with other software that allows for graphic presentations.

Baseline data will be summarised and listed.

**Definition of analysis populations**
The intention to treat population (ITT) is included in the full analysis set (FAS).

The ITT population will be constituted by 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 is basis for presentation of AEs and will be included in the safety analysis set (SAS).

The safety population constitute subjects who
- have given informed consent.

**Analysis of primary endpoint**
Sensor data will be graphically presented over time and sensor capability to generate a readable sensor profile will be visually evaluated (FAS) and considered versus what is known on bladder physiology.

In case of an unexpected profile, the sensor profile will be considered in relation to the data on urine flow and voided volume, obtained via a standard uroflow meter.

Readable sensor profiles versus non-readable sensor profiles will be summarized.

**Analysis of secondary endpoint**
Adverse events will be summarised and listed (SAS).

### 7.2. Sample size

Due to the conceptual nature of this trial no formal sample size calculation has been performed. It is assumed that 12 healthy volunteers will be adequate for evaluating the data quality of the sensor.

### 7.3. Drop-out

As this study only consist of one study visit, expected drop-outs are 0. Should there be a drop-out, will these be replaced until 12 patients has finalised visit 1.

### 7.4. Pass/fail criteria

No formal pass/fail criteria are applied.

### 7.5. Interim analysis

No interim analysis will be performed.

### 7.6. Statistical reason for termination of investigation

There is no reason to terminate the investigation based on statistical considerations

### 7.7. Deviation(s) from statistical plan

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

## 8. Data management

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

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

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

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

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.

# 9. Amendments to the CIP

Any significant changes to the CIP are:

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

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

# 10. Clinical Investigation Plan deviations

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

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

Deviations must be reported to sponsor and deviations affecting the scientific aspect of the investigation or the safety of the subject is reported to the EC and Danish Medicines Agency by sponsor. Deviations not affecting the scientific aspect of the investigation or the safety of the subject will be documented in a "Protocol deviation form" or a "Note To File" and filed in the Investigator Site File and Study Master File.

# 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.

The investigational site will receive 12 investigational devices – one for each subject and corresponding catheters.

The Investigator or a representative hereof keeps records documenting the receipt, use and return of the investigational devices.

## 12. Statement of compliance

The clinical investigation is conducted in accordance to:

- Ethical principles that have their origin in the Declaration of Helsinki, 1964, Last amended at the 64th WMA General Assembly, Brazil, 2013.
- MDD 93/42/EEC as amended by Directive 2007/47/EC (commonly known as the Medical Device Directive).
- MDR (EU) 2017/745
- ISO 14155:2011 "Clinical Investigation of medical devices for human subjects – Good clinical practices".

Any applicable regional or national regulations will be specified in the country specific CIP

### 12.1. Ethics committee and regulatory authorities

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

Sponsor will notify the relevant regulatory authority and EC(s) concerned of the end of the clinical investigation.

### 12.2. Other relevant authorities

### 12.3. Data protection

All information collected during this investigation is owned by Coloplast A/S and is kept strictly confidential. Subjects are identified by an investigation number and the investigation monitor has access to subjects' notes/documentation for source data verification. Monitoring and monitoring findings will be documented in a report to explain and document that the rights and well-being of the subjects are protected, that the reported data are accurate, complete and verifiable from source documents, and that the conduct of the investigation is following the currently approved Clinical Investigation Plan (CIP), including amendments, and with the applicable regulatory requirements. The reports have no subject identification and are kept confidential during the conduct of the investigation and during archiving for 6 years. Subjects remain anonym for data analysis, as the data is blinded correspondingly in the data analysis.

Should the investigation require future review, relevant ethics committees and Coloplast A/S Internal Audit performer will be allowed access to all relevant information for audit purposes.

The allowance of DKK 1200,- is taxable and will be payed to the subject after test visit as cash. The allowance is taxable per local legislations and Coloplast A/S is responsible for reporting the remuneration to the tax authorities. Therefore, it is necessary to collect subject's social security number and hand it over to tax authorities. The number will then be strictly confidentially handled, and only people with relevant interest will have access to the information.

Coloplast A/S complies with applicable data privacy law, including the EU General Data Protection Regulation ("GDPR"). Under GDPR the legal basis for Coloplast's collection and use of the personal information is for the purpose of analyzing samples, and all data collected in this clinical investigation.

Coloplast A/S protects all personal information and will only allow it to be used for the mentioned purposes related to only this clinical investigation.

Each subject is entitled to get access to all the data and to have rectified any inaccurate data Coloplast A/S is processing about the subject. All data are collected based on the consent each subject has given when being eligible and enrolled in the investigation. The subject is entitled to withdraw any such consent at any time, and Coloplast A/S will then cease to use such personal information for further innovation and improvement of incontinence products. The already data collected and handled in the investigation will not be retired.

For further information please see Coloplast's Global Privacy Notice (www.coloplast.com/global/privacy-notice)

### 12.4. Indemnity

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

[redacted]

### 12.5. Financial conditions

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

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

Subjects will be remunerated with [redacted] for the test visit. This is to compensate for any inconvenience caused during the catheterisations, time used and travel expenses. The allowance is taxable per local legislations and Coloplast A/S is responsible for reporting the remuneration to the tax authorities.

## 13. Informed consent process

Written informed consent is obtained from all subjects participating in the investigation after thorough written and verbal information. The information is given by the investigator or his/her representative in the subjects' native non-technical language. Each subject will be fully informed about the aim of the investigation, procedures, potential risks or inconveniences and/or expected benefits and have a minimum of 24 hours before deciding on participation. The subjects will be informed that their participation is voluntary and that they may leave the investigation at any time, without this having any influence on their further treatment.

The informed consent signature form includes personally dated signatures of the subject and the Investigator or a representative hereof responsible for conducting the informed consent process. A copy will be provided to the subject.

If new information is to be given during the investigation, sponsor will inform the investigators, and the new information is given to the subjects by the investigator. If new information becomes available that can significantly affect a subject's future health and medical care that information will be provided to the subject in written form. Clinical Manager is responsible for writing the information and providing it to investigators that will

further provide it to the subjects. If applicable, all affected subjects shall be asked to confirm their continuing informed consent in writing.

In addition, subjects will be asked to sign a Letter of Authority, consent to pass on social security number (CPR-number) to the Danish tax authorities, and a Secrecy Agreement.

[redacted]

## 14. Adverse events, serious adverse events and device deficiencies

### 14.1. Adverse event

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

### 14.2. Adverse device effect

An adverse event, which is related to the use of the investigational medical device, is an adverse device effect, and should be marked as related or possibly related on the adverse event form.

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

**Table 2 Anticipated adverse device effects and their likely incidence rates**

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

Definition of incidence rates are based on Coloplast A/S risk management system ratings (very unlikely 0-1%, unlikely 2-10%, occasional 11-50%, likely 51-90%, very likely 91-100%).

## 14.3. Device deficiency

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

## 14.4. 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.

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

### 14.4.1. 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.

### 14.4.2. Anticipated serious adverse device effect

There are no anticipated serious adverse device effects.

### 14.4.3. 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.

## 14.5. 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 physician in case of any adverse event(s) happening later than one week of investigation termination.

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

## 14.6. Reporting and timelines

### 14.6.1. Investigators reporting responsibilities

- PI at each site must assess all (S)AE`s that occur at his/her site.
- All serious adverse events and serious adverse device effects must be reported to sponsor within three calendar days.
- A device deficiency that could have led to a serious adverse event but did not because suitable action was taken, intervention had been made or because of fortunate circumstances should be reported to sponsor within three calendar days.
- New findings and/or updates in relation to already reported serious events should also be reported to sponsor within three calendar days.
- Device deficiencies and all adverse device effects must be reported to sponsor within 10 days.

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

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

### 14.6.2. 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 seven calendar days following the date of awareness by sponsor.

- All serious adverse events.
- All serious device effects.
- All device deficiencies that could have led to serious adverse events but did not because suitable action was taken, intervention had been made or because of fortunate circumstances.
- New findings and/or updates in relation to already reported events.

If the serious adverse event results in imminent risk of death, serious injury, or serious illness that requires prompt remedial action for other subjects, users or other persons or a new finding to such a serious adverse event, sponsor must immediately but no later than two calendar days after awareness by sponsor report the event to national regulatory authorities.

## 15. Suspension or premature termination of the clinical investigation

Sponsor may suspend or prematurely terminate an investigation site or the entire clinical investigation for documented significant reasons.

If a suspicion of an unacceptable risk to subjects develops during the clinical investigation, sponsor will suspend the investigation while the risk is assessed. Sponsor will terminate the investigation if an unacceptable risk is confirmed.

Sponsor will ensure that the premature termination will be justified in writing and will promptly inform the regulatory authorities and relevant ethic committee.

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

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

## 16. Clinical investigation report

At completion of the investigation sponsor is responsible for writing the clinical investigation report. The report is retained on file. The report contains a critical evaluation of all data, which have been collected during the investigation. The report describes the methodology and design and a data analysis, including statistical preparation and conclusion.

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

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

## 17. Publication policy

### 17.1. General

In connection with the publication policy Coloplast A/S is referring to the internal document 'Clinical Publication Policy' that will be available for internal and external persons involved in the publication process.

The investigation will be registered on a public accessible database before recruitment of the first subject. The results of the investigation, positive as well as inconclusive and negative will be published in the same public accessible database. The subjects' identity will remain confidential. Publication of results in the database will be conducted per the law of personal data protection and will be initiated as soon as scientifically acceptable, however, within one year after the last subject has completed the investigation. Data from the investigation is considered confidential until it is published per the conditions of this protocol and the 'Clinical Publication Policy'. Sponsor may publish anonymous single subject case stories (or public, if the subject consents) at any time during and after the investigation. The identification of the participant must not be possible. Sponsor reserves the right to use the data (published and unpublished) for reimbursement or regulatory purposes.

The results may be submitted to a scientific journal.

## 18. Bibliography

1. Investigators Brochure – CP304