# Clinical Investigation Plan

CP324

Exploratory investigation on performance and safety of newly developed intermittent catheters in female users of intermittent catheters

December 2020 - May 2021

NCT04557787

Document date: 2021Feb16

## CHANGE LOG

| VERSION NUMBER | ISSUED BY *(INITIALS)* | COMMENTS (MAJOR CHANGES SINCE LAST REVISION) |
|---|---|---|
| 1.0 | [redacted] | |
| 2.0 | [redacted] | • Specification of data protection, section 15.2.<br>• Specification of compensation for participating in the clinical investigation section 16.2. |
| 3.0 | [redacted] | • Specification of section 7.5 [redacted] |
| 4.0 | [redacted] | • Specification of recruitment strategy, section 6.2.1<br>• Specification of sample size, section 10.6 |
| 5.0 | [redacted] | • Specification of Subject recruitment, section 6.2.1, and Clinical investigation-related procedures, section 7.4 and Flowchart, section 7.8<br>• [redacted]<br>• Updated total expected duration of the clinical investigation due to the situation with COVID-19 (section 5.1, 5.9) |
| 6.0 | [redacted] | • [redacted] |
| 7.0 | [redacted] | • Updated section 6.2.1 to also include recruitment through a Coloplast database and advertisement, if needed.<br>• Updated the timeline. Due to COVID-19 the study start was postponed. |
| 8.0 | [redacted] | • Specification of section 6.2.1 (recruitment through Coloplast database) |

[redacted]

## SYNOPSIS OF THE CLINICAL INVESTIGATION

**Title:**

Exploratory investigation on performance and safety of newly developed intermittent catheters in female users of intermittent catheters

**Investigational devices and comparator:**

The two investigational devices are catheters for single use only and are intended to be used for drainage of the bladder through the urethra. The devices are intended to be used by intermittent catheter (IC) users in this clinical investigation, CP324. The investigational catheters (investigational device 1 and 2) and Comparator (SpeediCath® standard catheter) are classified as class I sterile device according to the Medical Device Directive, MDD 93/42/EEC, Rule 5.

**Aim, objectives and hypotheses of the clinical investigation:**

The aim of this investigation is to assess performance and safety of the two new female variants of intermittent catheters.

The primary objective is to:

- evaluate performance of the catheters

The secondary objectives are:

- to assess safety of the catheters
- to assess user experience with the catheters

Due to the exploratory nature of this investigation, no formal pass/fail criteria are applied. A positive as well as a negative outcome of any endpoint will provide knowledge that is useful in the further decision-making and development of the investigational device.

**Design of the investigation:**

This is a randomised, single blinded, cross-over investigation comparing two new catheters (investigational device 1 and 2) with a comparator catheter, respectively in 15 adult female IC users.

All included subjects will test both investigational devices and the comparator product during the investigation period with an interval of 4-14 days between each test (Visits 1-3). [redacted]

Hereafter the subject will return to a termination visit to return products, [redacted]

**Expected duration of the clinical investigation:**

The dates below are approximate, and no subjects will be enrolled before all required approvals have been obtained. If changes are required, applicable EC and regulatory authorities will be notified.

- FPI: Dec/Jan-2020/21
- LPI: Feb/Mar-2021
- LPO: Apr/May-2021

**Primary endpoint and secondary endpoints:**

The primary endpoint is volume of residual urine at 1st clogging per catheterisation (assessed by pressure sensor with time-logged scale or by collection of urine before/after first repositioning).

### Secondary endpoints

- Volume of residual urine post-catheterisation (assessed by ultrasound scan)
- Discomfort (overall, at insertion, during voiding, and at withdrawal) measured using VAS
- Number of adverse events

### Subjects

The clinical investigation will be conducted in 15 female IC users enrolled at multiple clinical investigation sites. With an aim to have 40-60% of the population being the sub-population with neurological bladder dysfunction, sufficient data will be obtained for data also to be applicable in this sub-population.

To be included in the investigation, the subjects must comply with the selection criteria described below:

### Inclusion criteria

| Inclusion criteria | Justification for inclusion criteria |
|---|---|
| 1. Female | |
| 2. Is at least 18 years of age and has full legal capacity | To meet Helsinki Declaration |
| 3. Has given written informed consent, signed letter of authority and signed secrecy agreement | To ensure voluntariness and that Helsinki Declaration is met. Letter of Authority is a demand from Danish Medicines and Health Authorities |
| 4. Should have used an intermittent catheter bladder management method daily, with at least 2 catheters used in average per day, during the last 3 months | To ensure standardisation of handling/training in intermittent catheters |
| 5. Ability to self-catheterise | To ensure standardisation of handling/training in intermittent catheters |

### Exclusion criteria

| Exclusion criteria | Justification for exclusion criteria |
|---|---|
| 1. Is breastfeeding | Even though the ingredients and the recipes have been approved for humans, their effect on embryos, foetuses, and infants are unknown. |
| 2. Is pregnant (based on pregnancy test - urine) | Even though the ingredients and the recipes have been approved for humans, their effect on embryos, foetuses, and infants are unknown. |
| 3. Participation in any other clinical study during this investigation | To eliminate uncertainty whether any Adverse Events (AE's) or Serious Adverse Events (SAE's) occurring during the investigation and to relate to use of the herein tested products. Also, to eliminate unintentional affect from other devices/medicines on the investigation's data. |
| 4. Symptoms of urinary tract infection as judged by the investigator | To ensure subject safety and integrity of results. |
| 5. Any know allergies towards ingredients in the products | Asked by competent authorities and to safeguard participating subjects. |
| 6. Relevant medical history that would prevent the subject to participate in the investigation (investigators judgement) | To ensure data will be obtained in the relevant population. |

### Investigation approval

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

## LIST OF ABBREBIATIONS

| ABBREVIATION | WRITTEN OUT | EXPLANATION |
|---|---|---|
| ADE | Adverse Device Effect | See section 17.2 |
| AE | Adverse Event | See section 17.1 |
| ASADE | Anticipated Serious Adverse Device Effect | See section 17.4.2 |
| CRF | Case Report Form (paper or electronic) | *Questionnaire to be used for data collection* |
| CM | Clinical Manager | |
| 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. |
| DD | Device deficiency | |
| EC | Ethical Committee | |
| FPI | First Patient In | |
| IB | Investigator's Brochure | Compilation of the current clinical and non-clinical information on the investigational medical device(s,) relevant to the clinical investigation. |
| IFU | Instruction for Use | |
| ITT | Intention to Treat | |
| LPI | Last Patient In | |
| LPO | Last Patient 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. |
| PP | Per Protocol | |
| SADE | Serious Adverse Device Effect | See section 17.4.1 |
| SAE | Serious Adverse Event | See section 17.4 |
| USADE | Unanticipated Serious Adverse Device Effect | See section 17.4.3 |

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# 1. List of personnel involved in the Investigation

## 1.1. Sponsor representatives

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

In case of emergency, please contact the Clinical Manager.

## 1.2. Investigator

| SITE 1 – DK001 PRINCIPAL INVESTIGATOR | |
|---|---|
| [redacted] | |

## 1.3. Other

All tasks done at the site, not done by the principal investigator, will be documented in the Site Personnel Signature and Delegation List.

# 2. Rationale/justification for conducting the clinical investigation

Urinary tract infections (UTIs) are a major problem in users of intermittent catheters [1-3]. Complete drainage of the bladder is considered key to maintain a healthy bladder and avoid UTIs [4, 5]. Intermittent catheterisation can cause trauma to the urethral tract, thereby inducing inflammation, which can ultimately lead to UTIs [6].

[redacted]

The aim of this investigation is to assess performance and safety of the two new female variants of intermittent catheters.

# 3. Objectives and hypotheses of the clinical investigation

## 3.1. Objectives

The primary objective is:

- to evaluate performance of the catheters

The secondary objectives are:

- to assess safety of the catheters
- to assess user experience with the catheters

## 3.2. Hypotheses

Due to the exploratory nature of this investigation, no formal pass/fail criteria are applied. A positive as well as a negative outcome of any endpoint will provide knowledge that is useful in the further decision-making and development of the investigational device.

# 4. Investigational devices and comparator

The two investigational devices are catheters for single use only and are intended to be used for drainage of the bladder through the urethra. The devices are intended to be used by female intermittent catheter (IC) users in this clinical investigation, CP324.

The investigational devices and Comparator (SpeediCath® standard catheter) are classified as class I sterile device according to the Medical Device Directive, MDD 93/42/EEC, Rule 5. Further information on the investigational device can be found in the Investigator's Brochure (IB) [8].

To ensure that the site has enough supplies, more products than needed will be provided by Sponsor to the site. All products will be accounted for both prior to and after use.

**Table 1: Overview of products needed in the investigation**

| Product | Description |
|---|---|
| Investigational device 1 – female participant | Intermittent catheter for female use |
| Investigational device 2 – female participant | Intermittent catheter for female use |
| Comparator – female participant | SpeediCath® standard Female |

## 4.1. Manufacturer of investigational devices

Responsible for manufacturing the investigational device:
Coloplast A/S
Holtedam 1
3050 Humlebæk
Denmark.

**Intended purpose of the investigational devices in the investigation**

The two newly developed investigational devices are urinary catheters for intermittent use. The catheters are intended for transient (less than 60 minutes) intermittent drainage of the bladder.

There are no proposed contraindications.

## 4.2. Identification, traceability and labelling of the investigational devices

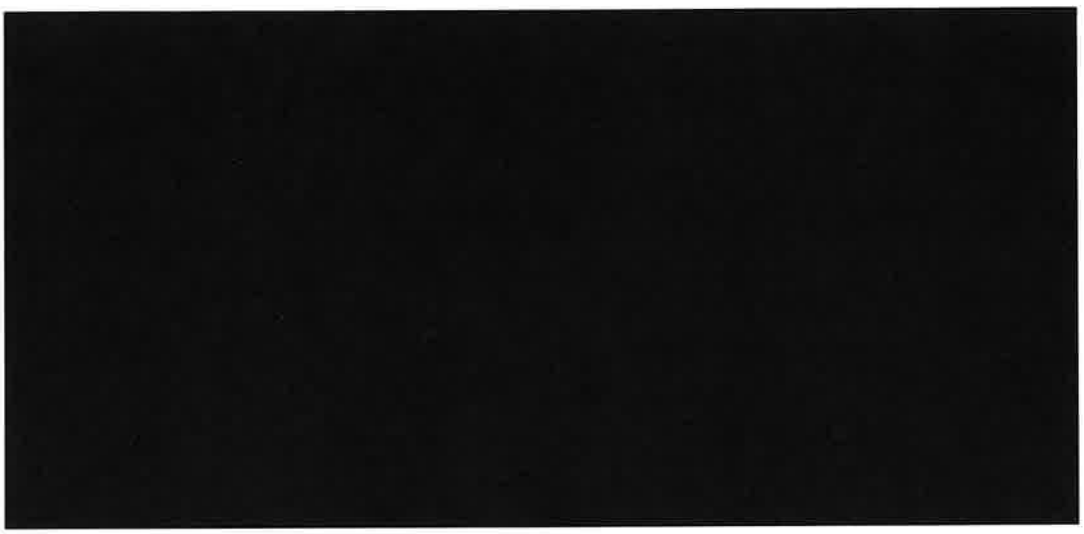

**Figure 1: Labels for the investigational devices for females, variant 1 and 2**

## 4.3. Intended population for the devices

Females who are depending on IC will be eligible to use the newly developed devices, when they become commercially available.

## 4.4. Handling and training

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

The devices should be stored at room temperature and away from direct sunlight, as described in the labelling.

For further details, please see the IB [8].

## 4.5. Description of the comparator product

As the comparator product is already on the market and will be used within the intended use in this investigation, it is not considered an investigational device according to ISO 14155:2011 and is thus not described here.

# 5. Design of the clinical investigation

## 5.1. General

This is a randomised, single blinded, cross-over investigation comparing the two new catheters (investigational device 1 and 2) with a comparator catheter, respectively in adult female IC users.

15 female IC users, of which the aim is to include 40-60% with neurological bladder dysfunctions, will be included in the investigation.

All included subjects will test both investigational devices and the comparator product during the investigation period with an interval of 4-14 days between each test (Visits 1-3). [redacted] Hereafter the subject will return to site to a termination visit [redacted]

[redacted]

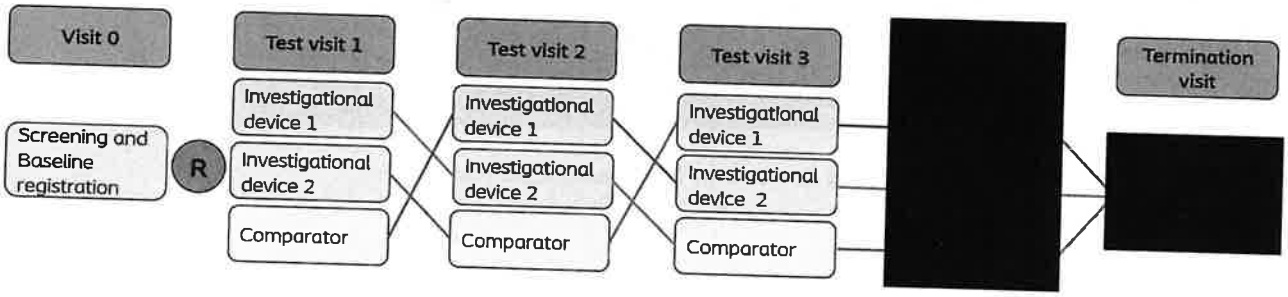


**Figure 1: Randomisation Scheme. See section 7.4 for details on the clinical investigation procedures. Abbreviations: R, randomisation**

The inclusion period is from December 2020 until March 2021, see section 5.9 for details on total expected duration of the investigation.

## 5.2. Primary endpoint

Volume of residual urine at 1st clogging per catheterisation (assessed by pressure sensor with time-logged scale or by collection of urine before/after first repositioning).

## 5.3. Secondary endpoints

- Volume of residual urine post-catheterisation (assessed by ultrasound scan)
- Discomfort (overall, at insertion, during voiding, and at withdrawal) measured using VAS
- Number of adverse events

## 5.4. Exploratory endpoints

- Number of incidents of urine running on the outside surface of the catheter
- Number of incidents of visual blood on the catheter post-catheterisation
- Number of incidents of positive haematuria measured with a dipstick post-catheterisation
- Number of incidents of positive leukocytes measured with a dipstick post-catheterisation

[redacted]

## 5.5. Rationale for selection and measurement of endpoints

Performance of the catheters will be measured by clogging events and the residual urine at first clogging in the bladder after catheterisation.

Macroscopic haematuria (visible blood), microscopic haematuria and leukocytes and discomfort are measured as indicators for safety of the catheters.

## 5.6. Demography and potential compromising factors

At baseline the age of the subject, concomitant medication and relevant medical history (IC relevant) will be collected. In addition, a total urine sample will be collected and analysed for [redacted] haematuria and leukocyte levels.

There are no restrictions for concomitant medication in the investigation. However concomitant medication should be noted, and the subject should not have changed their medication the last 24 hours before test visit 1-3 and during home use.

## 5.7. Randomisation Procedure

All subjects that meet the inclusion and exclusion criteria will be randomised to one of six treatment arms. Each arm examines the comparator product and each of the two investigational devices (Investigational device 1 and 2). The six possible arms are:

- Arm 1: Investigational device 1, Investigational device 2, and comparator
- Arm 2: Investigational device 2, Investigational device 1, and comparator
- Arm 3: Comparator, Investigational device 1 and Investigational device 2
- Arm 4: Comparator, Investigational device 2 and Investigational device 1
- Arm 5: Investigational device 2, Comparator and Investigational device 1
- Arm 6: Investigational device 1, Comparator and Investigational device 2

The randomisations list will consist of blocks of 6 and is centralised.

## 5.8. Blinding

Subjects will not be blinded in this investigation due to inclusion of self-catheterisation. Furthermore, personnel present at the catheterisation i.e. nurses and assisting Coloplast personnel are also not blinded. Coloplast personnel not present at the catheterisation i.e. the statistician will be blinded until the data base lock.

## 5.9. Total expected duration of the clinical investigation

The dates below are approximate, and no subjects will be enrolled before all required approvals have been obtained. If changes are required, applicable EC and regulatory authorities will be notified.

The test period for each subject is 14-70 days, due to the visit windows incorporated in the design of the investigation.

- FPI: Dec/Jan-2020/21
- LPI: Feb/Mar-2021
- LPO: Apr/May-2021

## 6. Clinical Investigation population

The clinical investigation will be conducted in 15 adult female IC users enrolled at multiple clinical investigation sites. The aim is to have 15 completers, and hence replacement will be made as appropriate as a sponsor decision. With an aim to have 40-60% of the population being the sub-population with neurological bladder dysfunction, sufficient data will be obtained for data also to be applicable in this sub-population.

### 6.1. Eligibility criteria

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

#### 6.1.1. Inclusion criteria

| Inclusion criteria | Justification for inclusion criteria |
|---|---|
| 1. Female | |
| 2. Is at least 18 years of age and has full legal capacity | To meet Helsinki Declaration |
| 3. Has given written informed consent, signed letter of authority and signed secrecy agreement | To ensure voluntariness and that Helsinki Declaration is met. Letter of Authority is a demand from Danish Medicines and Health Authorities |
| 4. Should have used an intermittent catheter bladder management method daily, with at least 2 catheters used in average per day, during the last 3 months | To ensure standardisation of handling/training in intermittent catheters |
| 5. Ability to self-catheterise | To ensure standardisation of handling/training in intermittent catheters |

#### 6.1.2. Exclusion criteria

| Exclusion criteria | Justification for exclusion criteria |
|---|---|
| 1. Is breastfeeding | Even though the ingredients and the recipes have been approved for humans, their effect on embryos, foetuses, and infants are unknown. |
| 2. Is pregnant (based on pregnancy test - urine) | Even though the ingredients and the recipes have been approved for humans, their effect on embryos, foetuses, and infants are unknown. |
| 3. Participation in any other clinical study during this investigation | To eliminate uncertainty whether any Adverse Events (AE's) or Serious Adverse Events (SAE's) occurring during the investigation and to relate to use of the herein tested products. Also, to eliminate unintentional affect from other devices/medicines on the investigation's data. |
| 4. Symptoms of urinary tract infection as judged by the investigator | To ensure subject safety and integrity of results. |
| 5. Any know allergies towards ingredients in the products | Asked by competent authorities and to safeguard participating subjects. |
| 6. Relevant medical history that would prevent the subject to participate in the investigation (investigators judgement) | To ensure data will be obtained in the relevant population. |

#### 6.1.3. Pregnancy and breastfeeding

For female subjects with childbearing potential (they have had at least one period during the last 12 months), a urine pregnancy test will be performed at the inclusion visit (V0) after signed informed consent, to ensure

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

The principal investigator must talk to the women about the risk of and how to avoid unwanted pregnancy at inclusion and at every test period the subject participates in hereafter.

If the subject is sexually active, she should be willing to practice appropriate contraceptive methods until the end of the investigation.
Appropriate contraceptive methods are:

- sexual abstinence (in some cases when the women are older than 50 years, but are not yet post-menopausal, the Principal Investigator may evaluate that it is not reasonable to ask these women to start using safe contraceptives for the duration of the investigation)
- oral contraceptives
- trans dermal patches
- depot injection of a progestogen drug
- double barrier method
- condom or occlusive cap (diaphragm or cervical/vault caps) plus spermicidal agent
- intrauterine device (IUD)
- intrauterine system (IUS)
- implant, or vaginal ring (placed at least 4 weeks before the first test period
- male partner sterilisation before the female participant's entry into the investigation and is the sole sexual partner for that female participant.

However, national requirements should always be followed.

If the subject becomes pregnant during the investigation, it is important, that the subject informs the principal investigator, or delegate, immediately. Hereafter the subject will be withdrawn from the investigation.

## 6.2. Recruitment and enrolment

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

If an eligible subject is interested in participating after the first contact, a visit will be arranged in a room reserved to ensure privacy and quiet surroundings at the investigators clinic/department. When arranging the visit, it will be ensured, that the subject has received and read the subject information prior to the visit. The subjects will receive both written and verbal information about the possibility of bringing a companion to the informational visit and to any possible subsequent visits.

### 6.2.1. Subject recruitment

The primary recruitment method will be through a subject record kept at site by the investigator. In this record potential subjects have, in connection with previously conducted trials at site, consented to be contacted for future trials conducted at this site. The investigator will from this subject record identify potential subjects in relation to the in- and exclusion criteria of this study.

When the investigator has identified a potential subject from the subject record, the investigator will contact the subject by sending them, by mail or e-mail, the Subject Invitation Letter attached the written subject information and "Forsøgspersoners rettigheder i et sundhedsvidenskabeligt forskningsprojekt", which they are encouraged to read. If the subject is interested in participating, she is encouraged to contact the site and an

information meeting is arranged. Follow-up by phone will be done by the site. (informed consent process, section 7.1 and clinical investigation-related procedures, section 7.4).

If needed, recruitment of subjects can also go through Coloplast's own subject database (intermittent catheter users) or by advertisements in e.g. local newspapers or relevant associations newspapers. The advertisement letter will include the contact information of the investigator or delegated study personnel (address, phone number and email address).

In the Coloplast database potential subjects are identified by the following search criteria: subjects who have consented to be contacted for future clinical investigations and e.g Intermittent catheter user, female and at least 18 years of age and diagnose. The identified potential subjects will as first contact be sent the advertisement letter by mail or email. The advertisement letter includes the contact information of the investigator or delegated study personnel (address, phone number and email address).

When a potential subject contacts the investigator or delegated study personnel, the investigator or delegated study personnel will give a short introduction to the investigation and go over the inclusion and exclusion criteria. If the subjects are eligible and still are interested in participating in the study an information meeting is arranged and the Subject Invitation Letter attached the written subject information and "Forsøgspersoners rettigheder i et sundhedsvidenskabeligt forskningsprojekt" will be sent to the subjects to ensure that they are given the opportunity to read about the investigation before the meeting.

Follow-up by phone will be done by Sponsor or by the site.

## 6.3. Subject withdrawal criteria

The subject can withdraw from the investigation at any time for whatever reason without any consequences for their future treatment outside the clinical investigation. 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:

- If subject's safety and wellbeing is compromised by further participation.
- Due to non-compliance with the Clinical Investigation Plan impacting the scientific integrity of the investigation
- Pregnancy (see section 6.1.3 Pregnancy and breastfeeding)

Replacements can be made as a sponsor decision. Replacements will be allocated to the same sequence as the withdrawn subject.

If a subject terminates the investigation before investigation completion, the subject will be informed to contact the site within the first week after termination in case of questions or issues they want to discuss related to this investigation. If they have questions more than a week after termination, they are informed to contact their practitioner.

## 6.4. 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 5.9.

### 6.5. Subject Identification and Confidentiality

Subjects will be identified on the electronic CRF (e-CRF) and any other document transmitted to the sponsor by the principal investigator or clinical site staff, by a unique identification number.

Data entered on the e-CRF are confidential and will only be available to the sponsor (including sponsor delegates), members of the EC and if requested to regulatory authorities.

The principal investigator for each clinical investigation site will maintain as part of the investigational file a list identifying all subjects entered the clinical investigation.

## 7. Procedures

### 7.1. Informed consent procedure

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. The clinical manager is responsible for writing the information and providing it to the investigators who 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.

### 7.2. Secrecy Agreement

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

At Coloplast A/S, the aim is to involve the IC users in testing the new catheter concepts. To develop a better product, it is essential for Coloplast A/S to get the user's experiences and comments to the new products as early as possible to receive valuable input for the further development.

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

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

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

## 7.3. Delegation of responsibility and training

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 investigational procedures, how to complete the case report forms (CRFs), procedure for reporting an adverse event (AE) or serious AE (SAE) (how, when, to whom), and who to contact in case of emergency related to the investigational devices. All training and delegation of tasks will be documented in the Clinical Investigation Training log and the Site Personnel Signature and delegation log.

## 7.4. Clinical investigation-related procedures

**Information meeting:**

- Subject information. After having received written and verbal information about participation in the investigation, the subject will be offered to have a minimum of 24 hours before deciding on participation (see Informed consent procedure, section 7.1)

**Visit 0 (Visit 0 may be completed the same date as visit 1. The subject must wait for 1-2 hours after drinking fluid):**

Screening:

- Informed consent, letter of authority and secrecy agreement signed
- In- and exclusion criteria fulfilled (incl. pregnancy test as applicable and dipstick for haematuria, leukocyte and UTI)
- Allocation of subject number and randomisation to order of treatment

Baseline registration:

- Demography (age)
- Concomitant medication
- Relevant medical history

Subject waits 1-2 hours after drinking fluid

- [redacted] Collection of total urine for analysis of [redacted]
  - Haematuria and leukocytes measured by dipstick

**Test visits 1-3 (Expected duration is approximately 3.5 hours per visit)**:

- Symptoms of UTI (The investigators Judgement)
- Catheterisation by nurse with relevant catheter (including pressure sensor and time-logged weighing of urine). Each catheterisation lasts approximately 15 minutes in total.
- Residual Urine measured (by ultrasound scan)
- Inspection of urine running outside the catheter
- Inspection of visual blood on catheter
- [redacted] Collection of total urine for analysis of [redacted]
  - Haematuria and leukocytes measured by dipstick
- Discomfort registered by subject (VAS scale) (insertion, during voiding, withdrawal, overall)
- The nurse evaluates the overall handling of the catheter

Subject waits 1-2 hours after drinking fluid

- Subject self-catheterises with relevant catheter (collection of urine before/after first repositioning including pressure sensor and time-logged weighing of urine)
- Residual urine measured (by ultrasound scan)
- Inspection of urine running outside the catheter
- Inspection of visual blood on catheter

[redacted] Collection of total urine for analysis of [redacted]

- Haematuria and leukocytes measured by dipstick

- Discomfort registered by subject (VAS scale) (insertion, during voiding, withdrawal, overall)
- The subject evaluates the overall handling of the catheter
- Registration of AE as applicable
- Schedule next visit (as applicable)

[redacted]

**Termination visit**

[redacted]

- Perform device accountability

[redacted] Collection of total urine for analysis of [redacted]

- Haematuria and leukocytes measured by dipstick

- Registration of AE as applicable
- Complete termination form

[redacted]

## 7.6. Rescheduling of visit

### 7.6.1. Suspicion of urinary tract infection

If the subject shows symptoms of UTI as judged by the investigator after she has been enrolled in the investigation, his visit can be rescheduled if possible and preferably before planned LPO visit, when the subject has been examined and treated for potential UTI and shows no symptoms afterwards. If it is not possible to complete all visits before LPO, the subject should complete as many visits possible allowed according to the investigation timelines.

### 7.6.2. Use of analgesics

Concomitant medication including analgesics should be noted, and the subject should not have changed their medication the last 24 hours before test visit 1-3 and during home use.

## 7.7. Activities performed by sponsor representatives

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

- Training of the investigator and investigational personnel in the informed consent procedure, investigation procedures, how to use the products, how to perform accountability of products, completing of the CRF, how to report possible safety issues and in ISO 14155. All training will be documented
- Support during the recruitment process and conduct of the investigation
- Measurements with pressure sensor
- Transportation of collected urine from site to Coloplast
- On site help with practicalities
- General support during the duration of the investigation
- Monitoring according to monitoring plan

[redacted]

## 7.8. Flow-chart

| | PER-FORMED BY | INFORMATION MEETING | V0 | V1 | V2 | V3 | [redacted] | TERMINATION VISIT |
|---|---|---|---|---|---|---|---|---|

| **Visit window** | - | The subject is offered to have a min. of 24 hours before deciding on participation | - | 0-21 days | 4-14 days | 4-14 days | 5-21 days | |
|---|---|---|---|---|---|---|---|---|
| **General** | | | | | | | | |
| Subject Information | Investigator | X | | | | | | |
| Signed Informed Consent | Subject | | X | | | | | |
| Signed letter of Authority and secrecy agreement | Subject | | X | | | | | |
| Check of in- and exclusion criteria | Investigator | | X | | | | | |
| Pregnancy test as applicable | Investigator | | X | | | | | |
| Allocation of subject number and randomization order | Investigator | | X | | | | | |
| Check subject's well-being and compliance with Clinical Investigation plan | Investigator | | X | X | X | X | | |
| **Registration of Baseline data** | | | | | | | | |
| Demography (age) | Investigator | | X | | | | | |
| Concomitant medication | Investigator | | X | | | | | |
| Relevant medical history | Investigator | | X | | | | | |
| Drink fluid and wait for approximately 1-2 hours | Subject | | X | | | | | |
| [redacted] | Subject | | X | | | | | |
| **Procedures** | | | | | | | | |
| Symptoms of UTI (Investigators Judgement) | Investigator | | | X | X | X | | |
| Catheterisation by nurse | Investigator | | | X | X | X | | |
| [redacted] | Investigator | | | X | X | X | | |
| Clogging events measured by sensor | Investigator / CP employee | | | X | X | X | | |
| Residual urine measured by bladder scan | Investigator | | | X | X | X | | |
| Inspection of visual blood on catheter | Investigator | | | X | X | X | | |
| Registration of urine running on the outside of catheter | Investigator | | | X | X | X | | |
| [redacted] | Investigator / CP employee | | | X | X | X | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Haematuria and leukocytes measured by dipstick (post-catheterisation) | Investigator | | | X | X | X | | |
| Discomfort registered by subject (VAS) post catheterisation | Subject | | | X | X | X | | |
| The nurse evaluates the overall handling of the catheter | Investigator | | | X | X | X | | |
| Drink fluid and wait for approximately 1-2 hours | Subject | | | X | X | X | | |
| Subject self-catheterises with relevant catheter | Subject | | | X | X | X | | |
| Residual urine measured (by ultrasound scan) | Investigator | | | X | X | X | | |
| [redacted] | Subject | | | X | X | X | | X |
| Inspection of urine running outside the catheter | Subject | | | X | X | X | | |
| Inspection of visual blood on catheter | Investigator | | | X | X | X | | |
| Haematuria and leukocytes measured by dipstick (post self-catheterisation) | Investigator / CP employee | | | X | X | X | | X |
| Discomfort registered by subject (VAS) self-catheterisation | Subject | | | X | X | X | | |
| The subject evaluates the overall handling of the catheter | Subject | | | X | X | X | | |
| Registration of any Adverse Events | Investigator | | | X | X | X | | X |
| Complete eCRF | Investigator | | | X | X | X | | X |
| Schedule next visit | Investigator | | | X | X | X | | |
| [redacted] | | | | | | | X | |
| [redacted] | Investigator | | | | | | | X |
| Perform device accountability | Investigator | | | | | | | X |
| **Registration of termination** | | | | | | | | |
| Complete Termination form | Investigator | | | | | | | X |

## 7.9. Case Report Forms

All assessments and observations throughout the investigation for each subject must be carefully recorded in an electronic CRF (eCRF) on a PC provided to the site by Coloplast.

Assessments completed by the investigator, or delegate, will be recorded in the eCRF.

CRFs will be completed by the investigator, or delegate, who has signed the Site Personnel Signature and Delegation List and Clinical Investigation Training Log.

It is the responsibility of the investigator that all data, measurements and observations are entered promptly and correctly and preferably immediately after the subject has been at site.

### 7.10. Supplementary materials and equipment

Supplementing devices or instruments normally used for catheterisation (e.g. medical gloves, tray for urine collection), scales for measurement of total amount of urine, ultra sound scanner measuring residual urine-container and funnel for urine collection and CE-marked commercially available SpeediCath® standard catheter acting as comparator and pressure sensor to measure cloggings.

The pressure sensor is an electronic device used for monitoring the pressure at the outlet of an intermittent urinary catheter voiding. The pressure sensor comprises a reusable electronic assembly and a single use adaptor which connects the catheter to the sensor. None of the sensor parts will have direct nor indirect contact to the end-user. The investigator is required to use gloves during the handling of the pressure sensor device during catheterisation.

The pressure sensor with the same functionality, hardware and specifications has previously been used in a Coloplast clinical investigation (CP304) [7].

## 8. Risk – benefit analysis and ethical considerations

The investigation is conducted in accordance with current law and applicable standards, see section 15. Statement of Compliance. The rights, safety and well-being of human subjects shall prevail over the interest of science of society.

The catheterisation of the subjects, with both investigational devices and the comparator catheter will be performed by experienced urology nurses at sites with many years of experience in conducting IC and with previous experience in working with clinical investigations.

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

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

Completed pre-clinical and clinical studies on the new catheter concept did not reveal any additional risks associated with the catheter prototypes [8]. 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 and leukocytes after catheterisation, which is expected to heal within 1-3 days. The investigational setting is not expected to result in increased frequency or severity of the known risks associated with urethral catheterisation.

## 9. Monitoring Plan

The sponsor is responsible for ensuring appropriate monitoring of the clinical investigation activities.

During the period of this investigation, monitoring is planned and carried out by the Clinical Managers.

The monitor (Clinical Manager) will be the primary contact for the investigator and clinical investigation site personnel.

Monitoring activities are mandatory as per good clinical practice, however the extend and depth of these activities depend on the criticality of the clinical investigation, speed of enrolment, the experience of the clinical investigation site personnel in carrying out clinical investigations and specific study designs.

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

## 9.1. Site selection visit

Depending on the prospective clinical investigation sites experience with the specific investigational device, an on-site qualification or site selection visit shall be performed during which the feasibility of the clinical investigation requirements will be discussed and common agreement between sponsor and the principal investigator shall be reached. This visit may also be replaced by one or more phone calls if the principal investigator is known to the sponsor.

## 9.2. Initiation visit

The clinical investigation site for this investigation will get an on-site initiation visit during which full training on all aspects of the clinical investigation will be provided.

## 9.3. Monitoring visits

The monitor is to ensure adherence to the clinical investigation plan, accurate data recording on the e-CRFs and to monitor recruitment rates and adherence to follow-up schedules. The investigator shall permit and assist the monitor to carry out verification of completed e-CRFs against data in the source documents.

The principal investigator can delegate tasks to his/her collaborators, however the roles and responsibilities as time of involvement for each clinical site personnel must be documented on the delegation log as well as training received before getting involved with the clinical investigation must be documented in the training log.

Before doing any review of subject data, the monitor must review the signed Informed Consent Form(s) and letter of authority and only monitor data from subjects with a correct signature on these forms. The monitor shall also be responsible for notifying such deficiencies in writing to the investigator and convene with the clinical investigation site personnel appropriate and timely corrective actions.

The first monitoring visit at the site should be conducted as soon as reasonably possible after the first subject(s) has(have) completed the first visit of the investigation. This is to minimise systematic errors done by site and to clarify potential questions before proceeding with enrolment of more subjects.

Additional monitoring will be conducted in accordance with the recruitment rate or if there is a need for more frequent visits upon request from site or Clinical Manager.

Written informed consent, in- and exclusion criteria and all AEs occurring in the investigation will be 100% verified for timely completion for all subjects enrolled in the investigation.
Investigation Site File shall be monitored for 100% completion per the Investigation File Requirement Checklist.
Monitoring activities will be documented in a site visit report. A follow up 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 (Clinical Manager) 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.

Close-out visit will be performed when all subject visits have been finalised, queries have been solved and database locked.

### 9.4. Source data verification

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

All documents and data related to the clinical investigation handled by site personnel, shall be produced and maintained in a way that assures reliability, integrity, control and traceability, and shall be appropriately stored to provide a complete history.

The Principal Investigator shall assure the accuracy, attribution, completeness, legibility and timeliness of the data reported to the sponsor in the eCRFs and in all required reports. All printed copies of electronic source documents shall be certified, as indicated by a dated signature by the investigational site personnel at the time the document is printed. Special requirements should be applied to the capture, review and retention of electronic source data, to ensure reliability, quality, integrity and traceability.

The data reported in the eCRFs shall be derived from source documents and be consistent with these source documents, and any discrepancies shall be explained in writing. In some cases, the eCRF can serve as the source document and this must be documented on the Source Data Specification Form. The Source Data Specification Form must be completed at the initiation visit detailing the location of the source data for each data point.

Data points for data verification:

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

The informed consent forms and Letter of Authority must be 100% verified for timely completeness.
Only the investigator, delegated site personnel and sponsor representatives will have access to all the CRFs.

### 9.5. Other methods for data quality assurance

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

## 10. Statistical considerations

All baseline assessments, endpoints and other measurements will be reported by descriptive statistics and/or listed. Endpoints, where data allows, will be analysed by catheterisation type i.e. nurse versus self-catheterisation. Summaries will, be presented by treatment, and if relevant, by other grouping variables.

Descriptive statistics for continuous variables are presented with N, Mean, SD (standard deviation), Median, Min and Max), where N denotes the number of subjects contributing with non-missing data. For discrete variables, descriptive statistics are presented with N and percentage, where percentage is based on the total number of subjects/observations with non-missing data.

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

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

## 10.1. Randomisation

This is a crossover investigation, where all subjects will be randomised into a pre-specified treatment sequence in a 1:1:1 treatment allocation ratio. For randomisation procedure, see section 5.7.

## 10.2. Blinding

Subjects will not be blinded in this investigation due to inclusion of self-catheterisation. Furthermore, personnel present at the catheterisation i.e. nurses and assisting Coloplast personnel are also not blinded. Coloplast personnel not present at the catheterisation i.e. the statistician will be blinded until the data base lock.

## 10.3. Definition of analysis populations

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

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

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

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

Individual endpoints/data points may be excluded from analysis, even though the corresponding subject belongs to the ITT population. This situation could arise due to protocol violations, where, at one visit, the primary endpoint could be affected, but same effect did not occur at any of the following visits.

All analysis will be based upon the ITT population and AEs will be summarised based on the safety population.

Any exclusion of subjects or data points from any of the populations must be documented.

## 10.4. Analysis of the primary endpoint

Volume of residual urine at 1st clogging per catheterisation (assessed by pressure sensor with time-logged weighing or by collection of urine before/after repositioning), will be analysed in a mixed model with subject included as a random component.

The model includes following fixed effects

Visit (visit 1, 2 and 3 of catheterisation)

Treatment (comparator (SpeediCath® standard), investigational device 1 and investigational device 2)

All treatment differences (catheters) as well as 95% confidence intervals will be estimated by using Proc Mixed in SAS. If relevant, other differences can be considered in the analysis.

## 10.5. Analysis of the secondary and exploratory endpoints

Following continues endpoints:

- Volume of residual urine post-catheterisation (assessed by ultrasound scan)
- Discomfort (overall, at insertion, during voiding, at withdrawal) measured using VAS

Will be analysed in a mixed model identical to the primary endpoint.

Following count and discrete endpoints:

[redacted]

- Number of incidents of urine running on the outside surface of the catheter
- Number of incidents of visual blood on the catheter post-catheterisation
- Number of incidents of positive haematuria measured with a dipstick post-catheterisation
- Number of incidents of positive leukocytes measured with a dipstick post-catheterisation

Will be analysed, in a negative binomial model, with effects identical to the primary endpoint model, using Proc Genmod or Glimmix in SAS.

The number of adverse events will be reported by descriptive statistics.

## 10.6. Sample size

Due to the exploratory nature of this investigation, no formal sample size calculation is performed.

A total of 15 subjects is deemed sufficient to evaluate safety and performance of the intermittent catheter prototypes.

In previous exploratory investigations, i.e. CP277, CP279 and CP290, very good indications on endpoints and hence, direction of product development, was achieved with relatively small sample sizes. In all three investigations, similar endpoints (discomfort, handling and trauma) and similar design (cross-over) were evaluated and sufficient information was gained by sample sizes in the range of 10-22 subjects (CP277: 30 subjects divided on 3 groups, CP279: subjects 22 and CP290: 10 subjects).

Also, in this investigation, we have a relatively small sample size of 15, but well within range of our earlier experience. And hence, we believe 15 subjects will provide the necessary insight and help guide the next step in product development.

A drop-out rate of 2-3 subjects is expected.

## 10.7. Pass/fail criteria

Due to the exploratory nature of this investigation, no formal pass/fail criteria are applied. A positive as well as a negative outcome of any endpoint will provide knowledge that is useful in the further decision-making and development of the investigational device.

## 10.8. Interim analysis

No interim analysis is planned.

## 10.9. Statistical reason for termination of investigation

There are no statistical reasons for terminating the investigation.

## 10.10. Deviation(s) from statistical design, method or analytical procedures

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

# 11. Data management

## 11.1. Data collection and data management

### 11.1.1. Data Collection in the clinical investigation

Data will be collected through an electronic data capturing (EDC) system on eCRF, a secure, internet based CRF. This system will be used to record all subject information collected in the investigation for secure data tracking and centralised data monitoring ("remote monitoring") done by monitors, as defined in the monitoring plan.

The EDC system used is Rave EDC, version 2018.2.2, delivered by Medidata Solutions Inc. The system is designed to be compliant with the FDA requirements of 21 CFR part 11. It is a validated data management system allowing only qualified and trained personnel to enter the system. The system has full audit trail and electronic signature.

The sponsor will be responsible for training the principal investigator, or delegate, in completion of the eCRF.

The principal Investigator, or delegate, at the clinical site will perform primary data collection directly into the eCRF or drawn from source-document (medical records, VAS, [redacted]) reviews. The eCRF will be completed on a continuous basis starting from the point of enrolling the subject to final follow up.

All assessments and observations throughout the investigation for each subject must be carefully recorded in an eCRF during the visit or immediately after.

When subject and the investigator are required to complete different sections in the CRF, it will be specified which sections the subject will fill in and which sections the investigator will fill in. Please see the flow chart in section 7.8 for details. If needed the investigator will assist the subject in completing the VAS.

In this study the part required to be completed by the subject is the pages regarding the endpoints measured by the VAS and [redacted]. These will be in Danish. After completion by the subject, the study nurse or the investigator will measure the VAS and enter the measurements into the eCRF.

In the unforeseen situation, where site cannot establish connection to the EDC system a paper CRF (pCRF) has been printed and supplied by sponsor.

The investigator will keep a separate list of the subjects' ID numbers, names and addresses in a locked room/cabinet. Only data referred to in this Clinical Investigation Plan will be recorded in the CRFs.

### 11.1.2. Database Management, Queries and Quality Control

The data management system has restricted role-based access control. The principal investigator or delegate must be trained in the system prior to getting access. The training is web-based and must be completed before access to the investigation is granted. Training will be documented in the data management system. Only the principal investigator, or delegate, will be authorised to enter data in the eCRF.

The monitor, using his/her personal login information shall verify all critical data points against the source documents and issue electronic queries for the authorised clinical site personnel to respond, as defined in the monitoring plan.

The principal investigator, using his/her personal login information, shall sign each eCRF.

Automated, real time access to the data enables control on investigation compliance and safety assessments. Automated alerts (e-mails) are generated by the system to ensure full control and easier compliance to the Clinical Investigation Plan.

A critical quality control will be performed by the sponsor's data management team and queries issued where needed. Such queries will be reviewed by the monitor and must be resolved by the site personnel.

[redacted]

At the end of the investigation a formal data review meeting will be performed before the database lock (DBL).

A full audit trail ensures, that each user's (site personnel, monitor, sponsor, data manager) access to and actions in the system is tracked.

Data management and the final statistical analyses of all measurements described in this clinical investigation plan are carried out by the Medical Affairs, Coloplast A/S.

### 11.2. Data retention

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

## 12. Amendments to the Clinical Investigation Plan

No changes in the clinical investigation procedures shall be affected without mutual agreement between the principal investigator and the sponsor. The agreement of the changes must be documented by signing the corresponding Clinical Investigation Plan amendments and registered in the Change Log.

All significant changes require notification to the Ethical Committee and applicable regulatory authority. Substantial changes may require approval from the Ethical Committee and applicable regulatory authority prior to implementation. (Example of significant change: Changes of inclusion criteria, end points or changes related to assessment methods.

## 13. Clinical Investigation Plan deviations

### 13.1. Deviations

Deviations to Clinical Investigation Plan occurs when the activities during the clinical investigation diverge from the Ethic committee approved investigation plan.
A deviation does not increase risk or decrease benefit or; does not have a significant effect on the subject's rights, safety or welfare; and/or on the integrity of the data.
Examples of deviations:

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

The investigator is not allowed to deviate from the Clinical Investigation Plan 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 Ethical Committee by sponsor.
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.

### 13.2. Violations

Violations to the Clinical Investigation Plan occurs when there is divergence from the Ethical Committee 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.

## 14. Device Accountability

All access to the investigational devices used in the clinical investigation is controlled by storage procedures and device accountability logs as described below. The investigational devices must only be used in this clinical investigation and only according to the Clinical Investigation Plan.

Sponsor keeps a device accountability log that states the physical location of all investigational devices from shipment of investigations devices to the investigational sites until return of or disposal.

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

- Subject identification.
- Identification of investigational device (batch no./serial no./unique code).
- The expiry date, if applicable.
- The date(s) of use, if possible.
- The date on which the investigational devices were returned (both used and unused if possible).
- Final accountability at the completion of the investigation.

## 15. 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 59th WMA General Assembly, Seoul, October 2008.
- 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 Clinical Investigation Plan.

## 15.1. Ethics committee and regulatory authorities

This Clinical Investigation Plan and/or other relevant documents are submitted to the appropriate Ethical Committee(s) and regulatory authorities. This clinical investigation will not begin until the required approval from the Ethical Committee and regulatory authorities have been obtained. Any amendment to the Clinical Investigation Plan will be submitted to the same Ethical Committee(s) and regulatory authority.

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

## 15.2. Data protection

As part of the investigation Coloplast A/S, Holtedam 1, 3050 Humlebaek, Denmark ("Coloplast") will collect and process the personal information the subject provides for the investigation ("subject personal data"). This includes identification and contact information (which may be anonymised depending on the nature of the investigation) as well as information about product usage experience and your health. Coloplast will comply with the EU General Data Protection Regulation (GDPR) and the Danish act on data protection ("databeskyttelsesloven"), including in connection with transfer of data to third countries, cf. chapter V of GDPR, Coloplast will only process the subjects' personal data:

1. To conduct the investigation and carry out related research based on subject consent (primary use), cf. articles 6(1)(a) and 9(2)(a) of GDPR ,
2. To comply with applicable legal obligations to e.g. ensure reliability and safety, cf. article 6(1)(c) in conjunction with article 9(1)(i) of GDPR, and
3. If separate consent is given for secondary use of subject personal data, cf. articles 6(1)(a) and 9(2)(a) of GDPR – carry out research outside the clinical protocol to improve Coloplast's products and services, and for use in education.

Part of Coloplast's processing is carried out on third-party platforms (clinical trial databases) and certain third parties are assisting Coloplast in the processing (e.g. the investigator). Such cases will imply a transfer of your personal data to the third parties, but solely for the specified purposes and with the third parties acting on instruction from Coloplast. Data may be collected and processed across the Coloplast network, which may entail processing of personal data outside the European Economic Area. In such cases, an adequate level of protection will be ensured by the third parties being subject to the standard contractual clauses on data protection adopted by the EU or to an EU-approved certification mechanism on data protection. For further information about this please the subject can always consult Coloplast's data protection officer (details below).

Subject personal data will be kept as long as required under applicable laws and regulations. The EU Medical Device Regulation obligates Coloplast to keep the data for a period of at least ten years after the investigation is completed, or, in the event that the device is subsequently placed on the market, at least ten years after the last device has been placed on the market. Subject personal data will be deleted at the end of the mandatory retention period.

If the subject has questions or queries regarding Coloplast's handling of personal information, the subject can always contact Coloplast's Data Protection Officer at dataprotectionoffice@coloplast.com. Complaints related

to Coloplast's handling of subject personal information may similarly be sent to the Data Protection Officer, and the subject is also entitled to file a complaint with the relevant supervisory authority, which in the case of Denmark is the Danish Data Protection Agency (www.datatilsynet.dk).

The subject can write to privacyrequests@coloplast.com at any time to request:

- Access to personal data
- Correction of errors in personal data or to erase personal data
- Limit what can be done with personal data
- To receive personal data in machine-readable format (data portability).
- Withdrawal of consents the subject has given Coloplast to process personal data

### 15.3. Financial conditions

Coloplast A/S will compensate all the investigators involved in the clinical investigation for their time and resources spent on the investigation. All financial agreements with the investigation sites involved in the clinical investigation will be specified in a sponsor investigator contract.

Investigator fee, excluding subject compensation, is estimated up to [redacted]. The investigator has no apparent conflict of interest.

## 16. Indemnity and Subject compensation

### 16.1. Indemnity

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

[redacted]

### 16.2. Compensation for participating in the clinical investigation

Subjects will be compensated with a voucher per visit to [redacted], paid by Coloplast A/S with the value as described below:

| | Subjects |
|---|---|
| [redacted] | [redacted] |

This is to compensate for any inconvenience caused during the catheterisations, time used. Travel expenses will be accounted for separately. The remuneration/vouchers are taxable (B-income) and it is the responsibility of the subject to declare this to SKAT.

## 17. Adverse events, adverse device effects and device deficiencies

### 17.1. Adverse events

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

### 17.2. Adverse device effect

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

The definition of an adverse device effect includes any event resulting from insufficiencies or inadequacies in the instruction for use, or any malfunction of the medical device, as well as any event resulting from use error or from intentional misuse of the device. Table 2 lists anticipated adverse device effects that may occur.

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

| ANTICIPATED ADES | LIKELYHOOD |
|---|---|
| Urinary tract infection | Very unlikely |
| Macroscopic haematuria | Unlikely |
| Macroscopic leukocytes | Unlikely |
| Stinging and pain in urethra during catheterisation | Likely |
| Irritation of mucosa | Likely |

### 17.3. Device deficiency

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

### 17.4. Serious adverse events (SAE)

A serious adverse event is an adverse event that:

- Led to death,
- Led to a serious deterioration in the health of the subject, users or other persons as defined by one or more of the following:
  1) a life-threatening illness or injury, or
  2) a permanent impairment of a body structure or a body function including chronic diseases, or
  3) in-patient or prolonged hospitalization, or
  4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
- Led to fatal distress, fatal 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 Clinical Investigation Plan, without serious deterioration in health, is not considered a serious adverse event.

### 17.4.1. Serious adverse device effect (SADE)

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

### 17.4.2. Anticipated serious adverse device effect (ASADE)

There are no anticipated SADEs.

### 17.4.3. Unanticipated serious adverse device effect (USADE)

An unanticipated serious adverse device effect is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

## 17.5. Medical care of subjects

The 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 the investigator if any AEs should occur during the investigation. Furthermore, the investigator will inform the subjects to contact him should SAEs occur within one week of the subject is terminated from the investigation. Subjects are informed to contact their general physician in case of any AEs happening later than one week of investigation termination.

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

## 17.6. Reporting and timelines

### 17.6.1. Investigator's reporting responsibilities

- The principal investigator at each site must assess all (S)AE`s that occur at his/her site.
- All serious adverse events and serious adverse device effects must be reported to sponsor within 24 hours of the site becoming aware of the event.
- A device deficiency that could have led to a serious adverse event but did not because suitable action was taken, intervention had been made or because of fortunate circumstances should be reported to sponsor within 24 hours of the site becoming aware of the event.
- New findings and/or updates in relation to already reported serious events should also be reported to sponsor within 24 hours of the site becoming aware of the event.
- Device deficiencies and all adverse device effects must be reported to sponsor within 10 days of becoming aware of the event.

When reporting the SAE, the relationship to the test material shall be described whether the event is considered

- **Not related**, the event has no temporal relationship with the use of the test material or the procedures.
- **Unlikely related**, the relationship with the use of the test material seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.

- **Possibly related**, the relationship with the use of the test material is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.
- **Probably related**, the relationship with the use of the test material seems relevant and/or the event cannot reasonably be explained by another cause, but additional information may be obtained.
- **Definitely related/Causal relationship**, the event has a temporal relationship with the test material use/application or procedures.

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 accessing e-mail is not possible, please call Clinical Manager, [redacted]

### 17.7. Sponsors reporting responsibilities

It is the responsibility of sponsor to ensure that the following are reported Danish regulatory authorities immediately, but no later than 7 calendar days following the date of awareness by sponsor.

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

If the serious adverse event results in imminent risk of death, serious injury, or serious illness that requires prompt remedial action for other subjects, users or other persons or a new finding to such a serious adverse event, sponsor must immediately but no later than 2 calendar days after awareness by sponsor report the event to Danish regulatory authorities

## 18. 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 EC(s). If monitoring or auditing of the clinical investigation identifies serious or repeated deviations at one of the participating investigation sites, sponsor will suspend or terminate the particular investigation site. The sponsor or the investigator will inform the regulatory authority as appropriate and notify 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 Clinical Investigation Plan for follow-up of the subjects as necessary.

## 19. 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.

The sponsor and the principal 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 should be obtained.

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

## 20. Publication policy

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

The investigation will be registered in a publicly accessible database, e.g. 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 publicly 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 Clinical Investigation Plan 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.

## 21. Suspension/termination of the clinical investigation

Sponsor will withdraw from sponsorship of the clinical investigation if

- major non-adherence to the Clinical Investigation Plan is occurring
- it is anticipated that the subject recruitment will not be adequate to meet the investigation objectives
- At least 75% of the subjects should be entered within the recruitment time.

In case sponsor withdraws, sponsorship for the subjects already recruited into the clinical investigation will continue.

## 22. Bibliography


1. Kennelly, M., et al., *Adult Neurogenic Lower Urinary Tract Dysfunction and Intermittent Catheterisation in a Community Setting: Risk Factors Model for Urinary Tract Infections.* Adv Urol, 2019. **2019**: p. 2757862.
2. Wyndaele, J.J., *Complications of intermittent catheterization: their prevention and treatment.* Spinal Cord, 2002. **40**(10): p. 536-41.
3. Bardsley, A., *Intermittent self-catheterisation in women: reducing the risk of UTIs.* Br J Nurs, 2014. **23 Suppl 18**: p. S20-9.
4. Vasudeva, P. and H. Madersbacher, *Factors implicated in pathogenesis of urinary tract infections in neurogenic bladders: some revered, few forgotten, others ignored.* Neurourol Urodyn, 2014. **33**(1): p. 95-100.
5. Merritt, J.L., *Residual urine volume: correlate of urinary tract infection in patients with spinal cord injury.* Arch Phys Med Rehabil, 1981. **62**(11): p. 558-61.
6. Vaidyanathan, S., et al., *Urethral cytology in spinal cord injury patients performing intermittent catheterisation.* Paraplegia, 1994. **32**(7): p. 493-500.
7. Clinical Investigational Report CP304 [redacted]
8. Investigators Brochure Nautilus CP324 [redacted]

## Appendix A [redacted]

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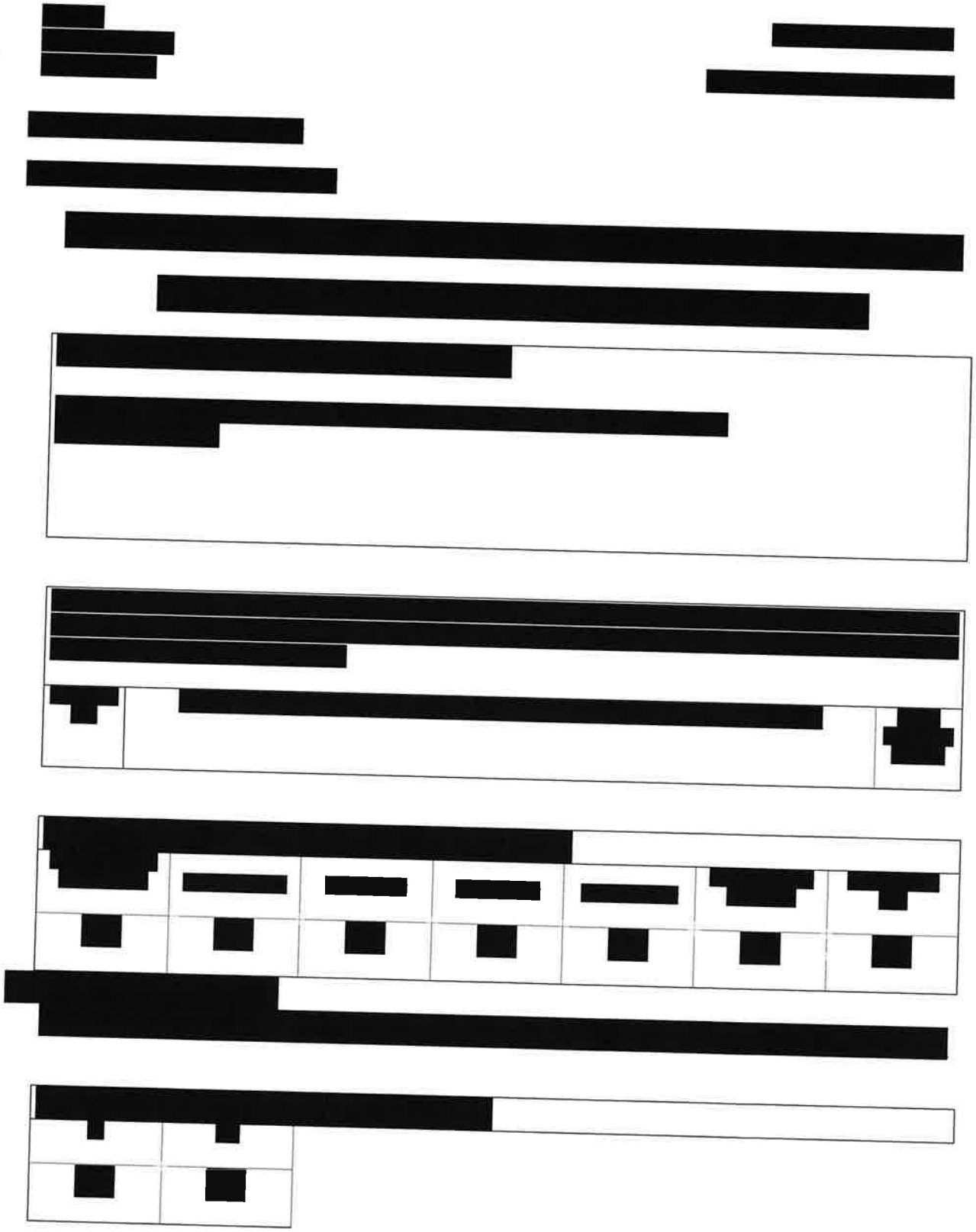

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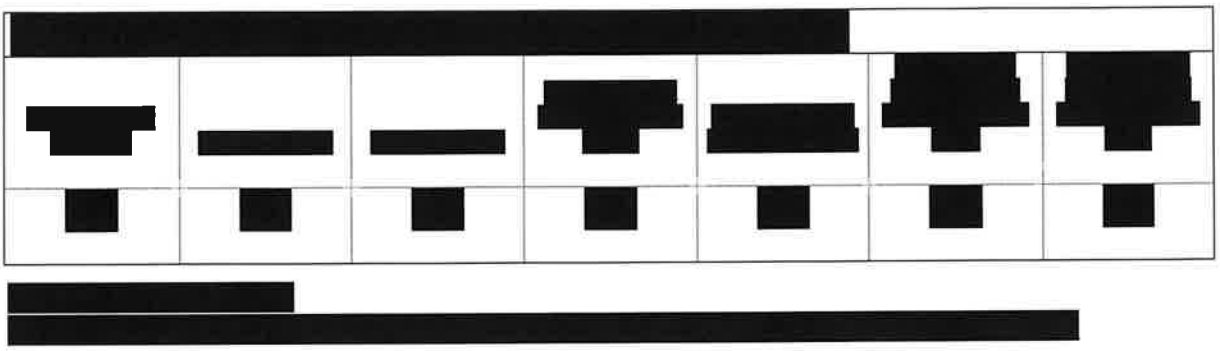

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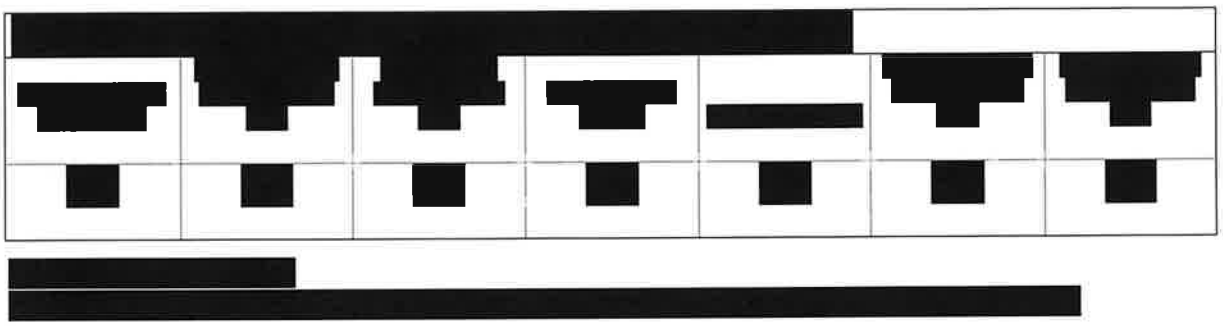

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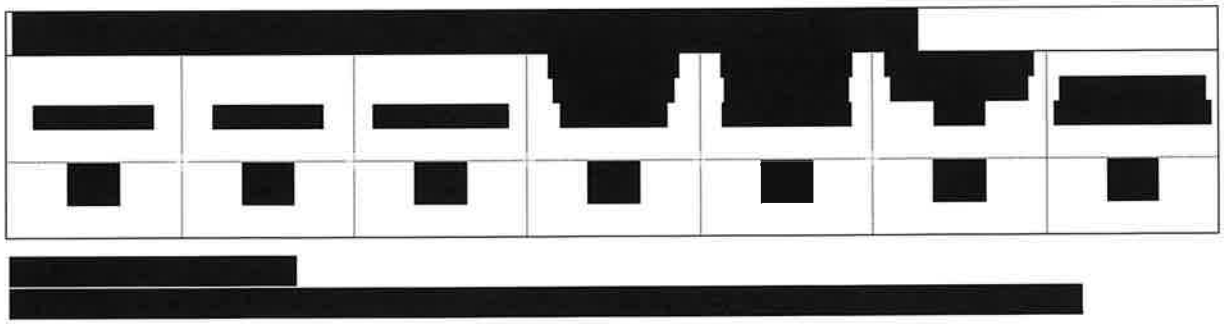

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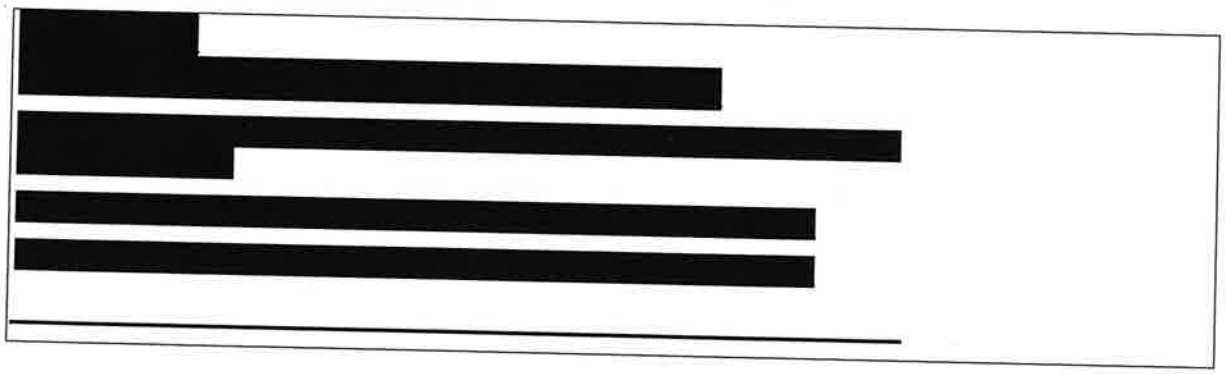

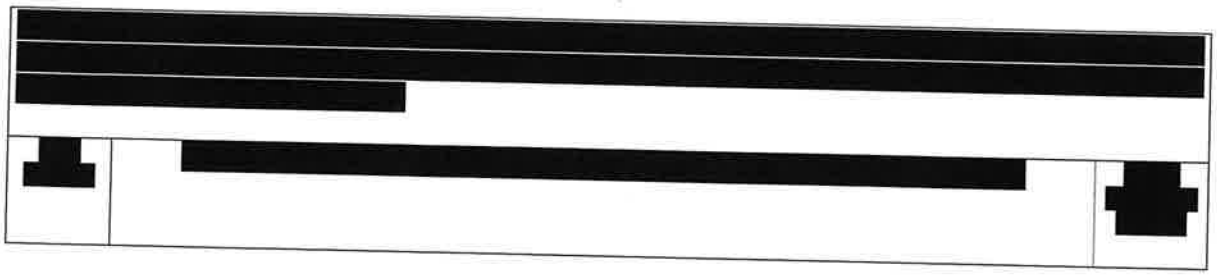

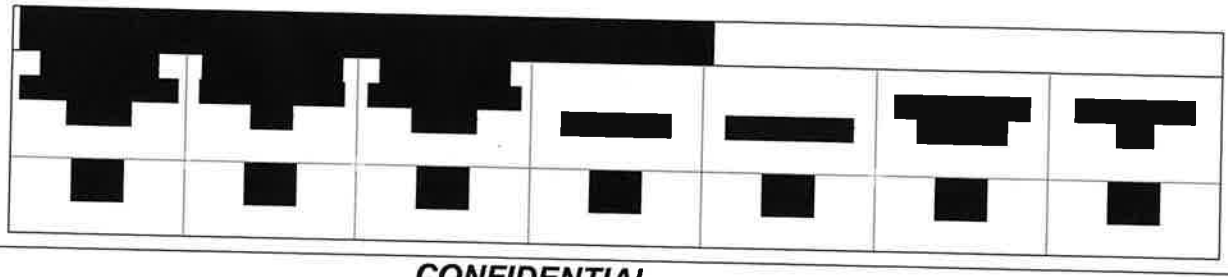

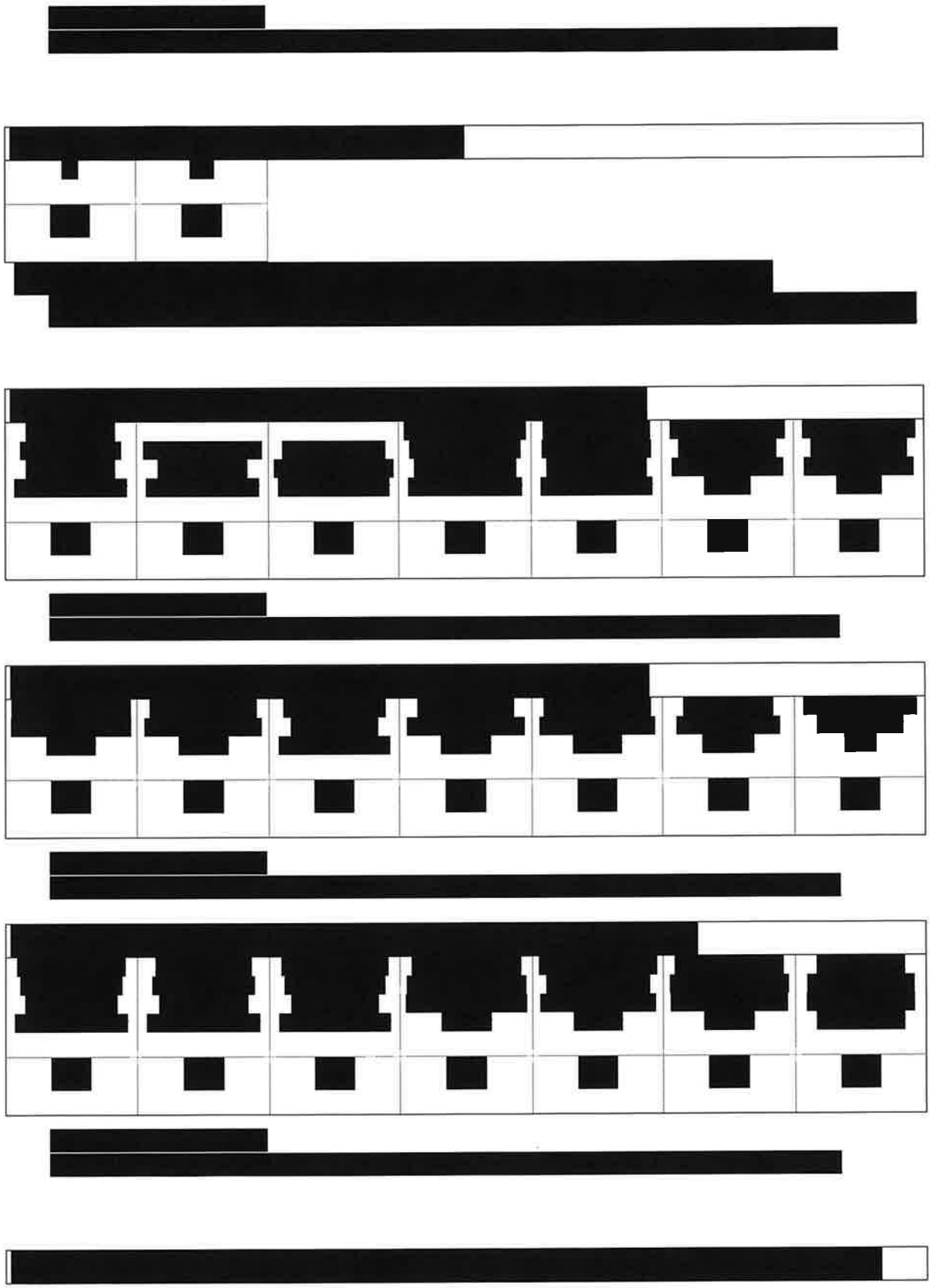

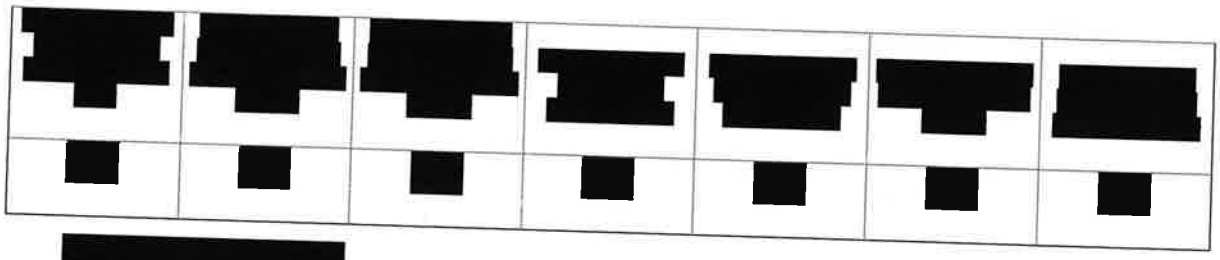

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## Appendix B: [redacted]

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