Clinical Investigation Plan

CP322

Exploratory investigation on performance and safety of new intermittent catheters in healthy volunteers

June 2020 – November 2020

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[redacted]

CHANGE LOG

VERSION NUMBER	ISSUED BY *(INITIALS)*	COMMENTS (MAJOR CHANGES SINCE LAST REVISION)
1.0	[redacted]	Document established in template version 7.0
2.0	[redacted]	4.3 and 4.4: Changes in secondary and exploratory endpoints 7.2: Changes in Clinical investigation-related procedures: Addition of baseline haematuria and leukocytes measurements
3.0	[redacted]	• Updated timeline of the clinical investigation due to the situation with COVID-19 • [redacted] Minor changes: • Addition of a separate section describing the collection of data on demography and potential compromising factors (section 4.6) and therefore the old section 7.7 `concomitant medication was deleted • Specification of one of the explorative endpoints (section 4.4) • Correction of section 4.5 • Corrections in the Flow-chart due to the above mentioned changes (section 7.7) • Specification of database management (section 10.1.2)

Objective

The primary objective is to evaluate performance of two newly developed catheters.

The secondary objectives are:

- to assess safety of the new catheters.
- to assess handling experience with the new catheters.

Design of the investigation

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 healthy volunteers.

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).

Primary endpoint and secondary endpoint(s)

Primary endpoint:

- Volume of residual urine at 1st clogging per catheterisation (assessed by pressure sensor with time-logged weighing)

Secondary endpoints:

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

Endpoints are per catheterisation.

Explorative endpoints:

- Handling experience (assessed by nurse)
- Number of incidents of visual blood on the catheter post-catheterisation
- Number of incidents of positive haematuria measured with a dipstick post-catheterisation and post-normal void
- Number of incidents of positive leukocyte measured with a dipstick post-catheterisation and post-normal void
- [redacted]
- Number of incidents of urine running on the outside surface of the catheter

Population

A total of 30 healthy volunteers, stratified by gender, will be included

Inclusion criteria
1. Is at least 18 years of age and has full legal capacity
2. Has given written informed consent and signed letter of authority and secrecy agreement
3. Willing to comply with not using analgesics[1] up to 24 hours prior to catheterisation visits
4. Negative urine multistix – erythrocytes (haematuria)

Exclusion criteria

1. Participation in any other clinical investigations during this investigation
2. Known hypersensitivity towards any of the test products
3. Symptoms of UTIs (Investigators judgement)
4. Pregnant or breastfeeding

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 users, and for this clinical investigation, CP322, by healthcare professionals for the healthy volunteer population.

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.

Investigation approval

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

List of abbreviations

ABBREVIATION	WRITTEN OUT	EXPLANATION
ADE	Adverse Device Effect	See section 15.2
AE	Adverse Event	See section 15.1
ASADE	*Anticipated Serious Adverse Device Effect*	*See section 15.4.2*
CIP	Clinical Investigation Plan	
(e)CRF	Case Report Form (paper or electronic)	Questionnaire to be used for data collection
CM	Clinical Manager	
DBL	Data Base Lock	Locking of the cleaned clinical data in the data base in the Data Base system (EDC)
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	
EDC	Electronic Data Capture	A software system designed for collecting clinical data in clinical trials. It consists of a data base for each clinical trial.
IB	Investigator's Brochure	Compilation of the current clinical and non-clinical information on the investigational medical device(s,) relevant to the clinical investigation.
IC	Intermittent Catheterisation	
IFU	Instruction for Use	
ITT	*Intention to Treat*	
PI	Principal Investigator	Qualified person responsible for conducting the clinical investigation at an investigation site. If the clinical investigation is conducted by a team of individuals at an investigation site, the PI is the responsible leader of the team. Whether this is the responsibility of an individual or an institution can depend on national regulations.
PP	*Per Protocol*	
SADE	Serious Adverse Device Effect	See section 15.4.1
SAE	Serious Adverse Event	See section 15.4
USADE	Unanticipated Serious Adverse Device Effect	See section 15.4.3
UTI	Urinary Tract Infection	

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1. List of personnel involved in the Investigation

1.1. Sponsor representatives

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

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. Introduction

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 (IC) 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 evaluate performance and safety of two newly developed intermittent catheter prototypes.

3. Objectives and hypotheses of the investigation

3.1. Objectives

The primary objective is to evaluate performance of the new catheters.

The secondary objectives are:

- to assess safety of the new catheters.
- to assess handling experience with the new 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. Design of the investigation

4.1. General

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

A total of 30 healthy volunteers, stratified by gender, will be included.

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), see randomisation scheme below.

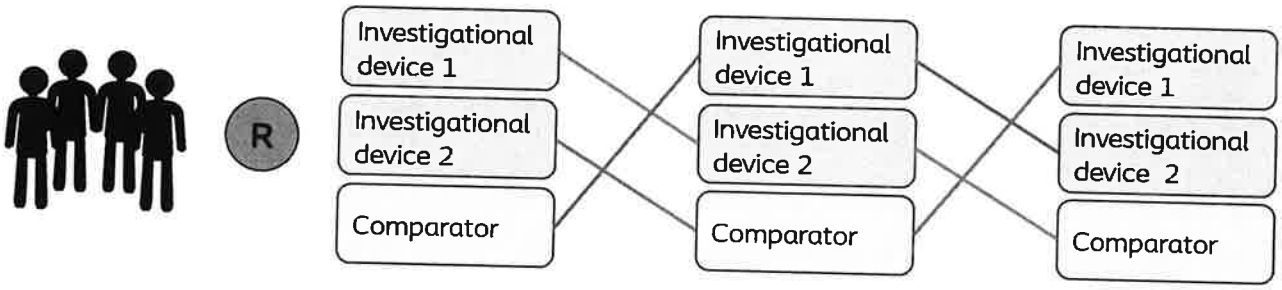

Figure 1: Randomisation Scheme. Abbreviations: R, randomisation

For details on investigation procedures – see section 7, Procedures.

In the investigation, male participants will form an interim population. Hence, enrolment should facilitate completion of all male subjects as soon as possible.

The inclusion period is from June 2020 until October 2020. The test period for each subject can be up to 42 days, due to the visit windows incorporated in the design of the investigation. The last patient out (LPO) will be during November 2020.

4.2. Primary endpoint

- Volume of residual urine at 1st clogging per catheterization, assessed by a pressure sensor with time-logged weighing.

4.3. Secondary endpoints*

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

* Endpoints are per catheterisation.

4.4. Explorative endpoints:

- Handling experience (assessed by nurse)
- Number of incidents of visual blood on the catheter post-catheterisation
- Number of incidents of positive haematuria measured with a dipstick post-catheterisation and post-normal void
- Number of incidents of positive leukocyte measured with a dipstick post-catheterisation and post-normal void
- Number of incidents of urine running on the outside surface of the catheter

4.5. Rationale for selection and measurement of endpoints

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

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

4.6. 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 haematuria and leukocyte levels.

There are no restrictions besides the use of analgesics prior to 24 hours before the test visits.

5. Investigational devices and the comparator

5.1. Description of the investigational devices

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 products are intended to be used by IC users, and by healthcare professionals on subjects in this investigation, CP322.

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 – male participant	Intermittent catheter for male use
Investigational device 1 – female participant	Intermittent catheter for female use
Investigational device 2 – male participant	Intermittent catheter for male use
Investigational device 2 – female participant	Intermittent catheter for female use
Comparator – male participant	SpeediCath® standard Male
Comparator – female participant	SpeediCath® standard Female

5.1.1. Manufacturer of investigational devices

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

5.1.2. Identification, traceability and labelling of the investigational devices

The investigational devices will be labelled on the individual product for identification and traceability.

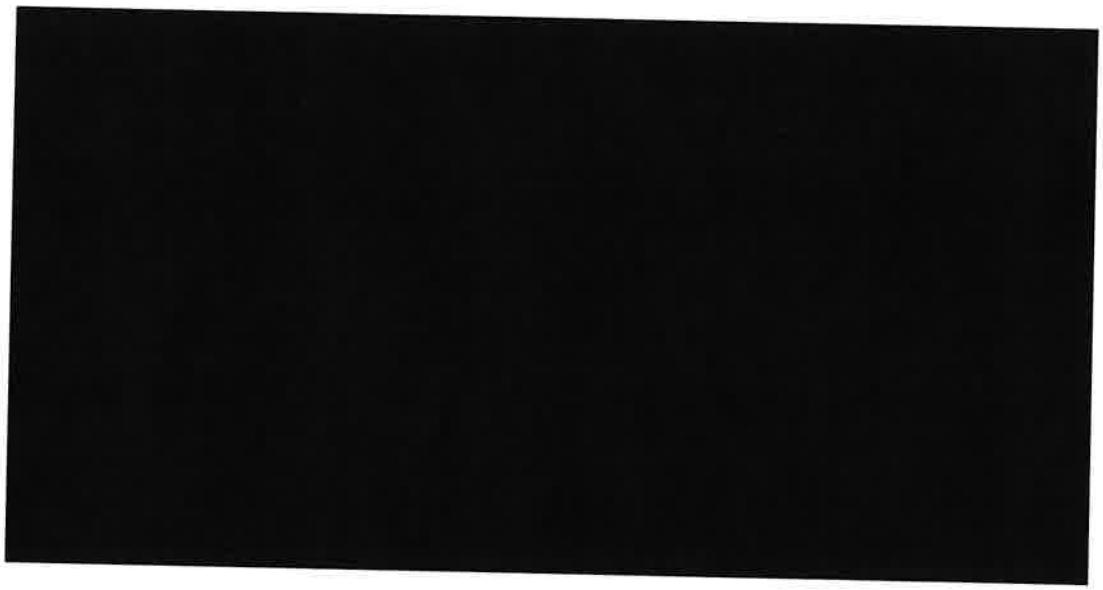

Figure 2. Labels for the investigational devices for males, variant 1 and 2

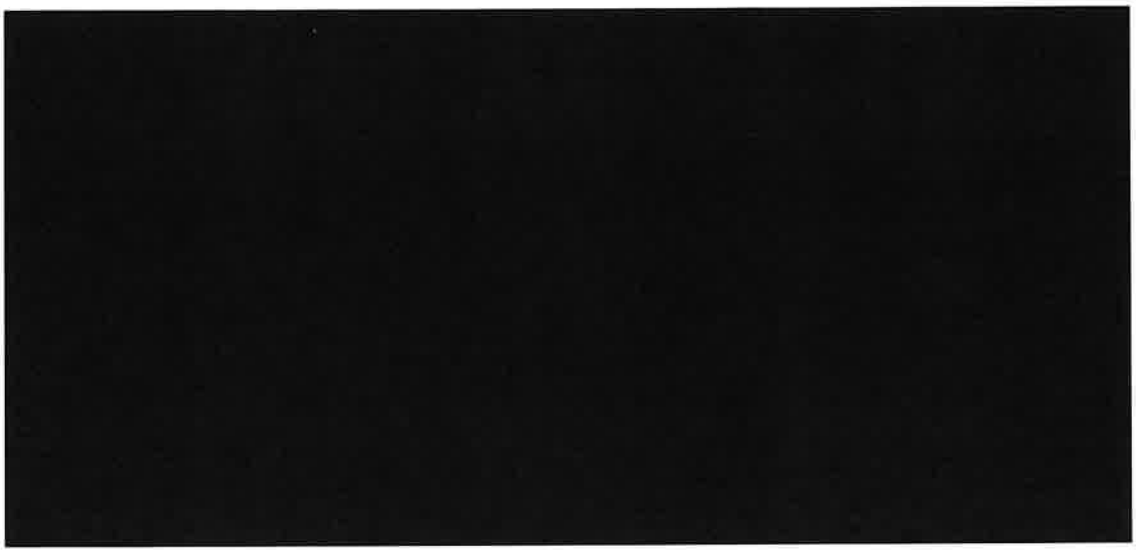

Figure 3. Labels for the investigational devices for females, variant 1 and 2

5.2. Intended purpose of the investigational device 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.

5.3. Intended population for the devices

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

5.4. 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].

5.5. Risks and benefits of the investigational devices and the investigation

The investigation is conducted in accordance with current law and applicable standards, see section 14. 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 from [redacted] 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 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.

5.6. 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.

6. Subjects

30 healthy volunteers stratified by gender will be enrolled.

6.1. Inclusion and exclusion criteria

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

6.1.1. Inclusion criteria

Inclusion criteria	Justification for inclusion criteria
1. Is at least 18 years of age and has full legal capacity	To meet Helsinki Declaration
2. 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
3. Willing to comply with not using analgesics up to 24 hours prior to catheterisation visits	Pain relief could affect primary and explorative endpoints and general experience of catheterisation. The 24 hours are chosen based on use of most common analgesics (Ibuprofen, paracetamol and aspirin) which have a half-life (T½) of two hours. Using safety equation of T½ x five hours gives ten hours, where 3% is left in the body. The 24 hours is given as safety margin and is more practical in the investigation
4. Has a negative urine multistix for erythrocytes (microscopic haematuria) Definition of negative/positive results for Multistix erythrocytes: Negative: Negative. Non-haemolysed 10 Ery/µL (+/-) Haemolysed 10 Ery/µL (+/-) Positive: Non-haemolysed 80 Ery/µL (2+) Haemolysed 25 Ery/µL (1+) Haemolysed 80Ery/µL (2+) Haemolysed 200 Ery/µL (3+)	Haematuria is an explorative endpoint. If subjects have haematuria when entering the investigation, it could affect the evaluation of data. Haematuria could also be a sign of Urine Tract Infections (UTI) which is also an exclusion criterion

6.1.2. Exclusion criteria

Exclusion criteria	Justification for exclusion criteria
1. Participation in any other clinical investigation 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.
2. Known hypersensitivity towards any of the test products	Asked by competent authorities and to safeguard participating subjects.
3. Symptoms of UTIs (Investigators judgement)	
4. Pregnant or breastfeeding	Even though the ingredients and the recipes have been approved for humans, their effect on embryos, foetuses, and infants are unknown.

6.2. 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 (Visit 0), to ensure the subject is not pregnant. The urine pregnancy test will be performed by dipstick at the investigation site. Furthermore, females should not be breastfeeding when participating in the clinical investigation.

6.2.1. Contraception strategy

Adequate contraception of females of child-bearing potential considered to be adequate include:

- Intra-uterine device
- Hormonal contraception
- Double barrier (condom together with a contraceptive diaphragm or cap)
- Sterile partner(s)
- Sexual abstinence

Females are considered to be of non-child-bearing potential if sterilised (by surgical means) or post-menopausal (defined as 12 months without a bleeding episode).

6.3. 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.

6.3.1. Subjects recruited via subject records

Investigator identifies potential subjects in relation to in- and exclusion criteria through subject records kept at the site (from previous clinical studies involving healthy subjects) where the subjects have consented to be contacted for future trials [redacted]. The identified potential subjects will receive by mail or e-mail the Subject Invitation Letter attached the written subject information and "*Forsøgspersoners rettigheder i et sundhedsvidenskabeligt forskningsprojekt*" which they are encouraged to read. If the subject is interested in participating, he/she is encouraged to contact the site and visit 0 is arranged. Follow-up by phone will be done by site. (informed consent process, see section 7).

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

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

6.4. Subject withdrawal criteria

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

The investigator must withdraw a subject from the investigation due to:

- If subject's safety and wellbeing is compromised by further participation.
- Noncompliance with the Clinical Investigation Plan (CIP) impacting the scientific integrity of the investigation
- Pregnancy.

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.

6.5. Point of enrolment

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

6.6. Total expected duration of the investigation

The dates below are approximate, and no subjects will be enrolled before all required approvals have been obtained. Changes greater than ± 3 months will be notified to EC and regulatory authorities.

- First subject enrolled (06/2020).
- Last subject enrolled (10/2020).
- Last subject completed (11/2020).

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 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.

7.1.1. 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 user 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 tof 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.

7.2. Clinical investigation-related procedures

Before initiation of the clinical investigation, sponsor must be provided with key personnel signed and dated curriculum vitae (not more than 2 years old) to verify their qualifications. Key site personnel are those, who treat or evaluate subject data in the clinical investigation. Also, the sponsor will ensure that all site personnel are trained in the 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.

Visit 0:

Screening:

- Subject information
- 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, gender)

- Concomitant medication
- Collection of total urine for analysis of [redacted]

Test visits 1-3 (visit 1 may be completed the same date as visit 0. The subject must wait for 1-2 hours after drinking fluid):

- Haematuria and leukocytes measured by dipstick, before catheterisation
- 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)
- Collection of total urine for analysis of [redacted]
    - Haematuria and leukocytes measured by dipstick
    - Inspection of urine running outside the catheter
    - Inspection of visual blood on catheter
    - Symptoms of UTI (Investigators Judgement)
- Discomfort registered by subject (VAS scale) (insertion, during catheterisation, withdrawal, overall)
- Evaluation of overall handling by nurse
- Subject waits 1-2 hours after drinking fluid
- Collection of total urine for analysis of [redacted]
    - Haematuria and leukocytes measured by dipstick
- Discomfort registered by subject (VAS scale) (overall, during voiding)
- Registration of adverse events as applicable
- Schedule next visit (only applicable for Visits 1 and 2)
- Complete termination form (Only applicable for Visit 3)

All catheters used at the visits will be saved for accountability.

[redacted]

7.4. Rescheduling of visit

7.4.1. Suspicion of urinary tract infection

If the subject shows symptoms of UTI (Investigators judgement) after he/she has been enrolled in the investigation, he/she will be referred to his own physician for further examination. When the subject has been examined and treated for potential UTI, and shows no symptoms afterwards, his/her visit can be rescheduled if possible and preferably before planned LPO visit. 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.

7.4.2. Use of analgesics

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

7.5. Activities performed by sponsor representatives

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

- Training of 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 [redacted]
- On site help with practicalities
- General support during the duration of the investigation.
- Monitoring according to monitoring plan.

7.6. Flow-chart

	PERFORMED BY	BASELINE V0	V1	V2	V3 TERMINATION VISIT
Visit window	-	-	0-14 days	4-14 days	4-14 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			
Allocation of subject number and randomisation order	Investigator	X			
Pregnancy test if applicable	Investigator	X			
Dipstick for haematuria, leukocyte and UTI	Investigator	x	X	X	X
Check subject's well-being and compliance with CIP	Investigator	X	X	X	X
Registration of Baseline data					
Demography (age, gender)	Investigator	X			

Concomitant Medication	Investigator	X			
[redacted]	Subject	X			
Procedures					
Symptoms of UTI (Investigators Judgement)	Investigator	X	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
[redacted]	Investigator / CP employee		X	X	X
Haematuria measured by dip-stick (post-catheterisation)	Investigator	X (part of the inclu-sion criteria)	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
Discomfort registered by sub-ject (VAS) post catheterisation	Subject		X	X	X
Evaluation of overall handling of catheter	Investigator		X	X	X
Drink fluid and wait for approxi-mately 1-2 hours	Subject		X	X	X
[redacted]	Subject		X	X	X
Haematuria measured by dip-stick (post voiding)	Investigator / CP employee		X	X	X
Discomfort registered by sub-ject (VAS) post voiding	Subject		X	X	X
Registration of any Adverse Events	Investigator		X	X	X
Complete eCRF	Investigator		X	X	X
Schedule next visit	Investigator		X	X	
Registration of termination					
Complete Termination form	Investigator				X

7.7. 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 principal investigator, or delegate, will be recorded in the eCRF.

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

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

7.8. 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. 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. 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 letter of authority and only monitor data from subjects with a correct signature on these forms.

The first monitoring visit (MV1) 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 conducted by the Clinical Manager 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 principal 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.

8.1. 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 describing the detailed location of the source data for each data point collected.

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.

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

All data collected can be directly entered into the CRF making the CRF the source. In case sites write source data in medical records or nurse notes, this will be described in the site specific "source data specification form".

Where no source data (besides the CRF) is available the contents of the CRF will be monitored.

8.2. 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.

9. Statistical considerations

All baseline assessments, endpoints and other measurements will be reported by descriptive statistics and/or listed. Summaries will be presented by treatment and gender, 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).

9.1.1. Randomisation

As this is a crossover investigation, all subjects will be assigned all three treatments in a 1:1:1 allocation ratio, where each subject will be randomised into a pre-specified treatment sequence.

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

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

9.1.2. Blinding

A single blinding will be implemented. Subjects will be blinded with a curtain and will not be able to see the catheter used. The personnel present at the catheterisation i.e. nurses and assisting Coloplast personnel are not blinded and Coloplast personnel not present at the catheterisation i.e. the statistician will be blinded until the data base lock.

9.2. 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, with valid information on at least one endpoint.

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.

9.3. Analysis of the primary endpoint

Volume of residual urine at 1st clogging per catheterisation (assessed by pressure sensor with time-logged weighing), 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)*Gender (male and females)

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.

For the interim analysis, gender is not included in the model, as the investigational population at the interim consists of male subjects only.

9.4. 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 catheterisation, at withdrawal and at the next normal void) measured using VAS.

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

Following discrete endpoints

- Number of clogging incidents per catheterisation (assessed by pressure sensor)
- 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 and post-normal void
- 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

9.5. Sample size

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

A total of 30 subjects is deemed sufficient to evaluate safety and performance of the intermittent catheter prototypes – where the 30 subjects are equally divided between males and females

A drop-out rate of 2-3 subjects within each gender is expected and subjects will be replaced.

9.6. 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.

9.7. Interim analysis

An interim analysis is planned by completion of the male subjects.

9.8. Statistical reason for termination of investigation

The interim analysis is constituted by male subjects only, where after the investigation continues with females. Hence, there is no statistical reasons for terminating the investigation, as blinding is fully maintained for both males and females.

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

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

10. Data management

10.1. Data collection and data management

10.1.1. 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.

Principal Investigator, or delegate, at the clinical site will perform primary data collection directly into the eCRF or drawn from source-document (medical records) 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 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 7.6 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 solely the pages regarding the endpoints measured by the VAS. These pages will be in Danish. After completion by the subject, the study nurse or 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.

10.1.2. **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 CIP.

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 CIP are carried out by the Medical Affairs, Coloplast A/S.

10.2. Data retention

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

11. Amendments to the CIP

Any significant changes to the CIP will be:

Agreed between sponsor and the principal 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 Ethical Committee before implementation.

Notified to or approved by the regulatory authorities before implementation.

Example of significant changes: Changes of inclusion criteria, end points or changes related to assessment methods.

12. Deviations from Clinical Investigation Plan

Deviations to CIP occurs when the activities during the clinical investigation diverge from the approved CIP. The Investigator is not allowed to deviate from the CIP unless there is an emergency circumstance and if the purpose of the deviation is 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 and regulatory authorities by sponsor if required by national regulations.

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.

In case of continued or repeated deviations affecting the scientific aspect of the investigation or the subjects' rights, safety and well-being sponsor will re-train the site personnel and PI and in worst case disqualify the PI from further participation in the investigation.

For this investigation the site personnel will be asked after each visit if they have been compliant to the protocol. If they have not, a deviation form will automatically be initiated in the eCRF where the site will have to describe the deviation. All deviations will be collected in one database and reviewed on an ongoing basis.

13. 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 CIP.

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

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

Date of receipt.

Subject identification.

Identification of each 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).

Final accountability at the completion of the investigation.

14. 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".

14.1. Ethics committee and regulatory authorities

The CIP and/or other relevant documents are submitted to the appropriate Ethical Committees 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 protocol will be submitted to the same Ethical Committees and regulatory authority.

Sponsor will notify the relevant regulatory authority and Ethical Committees about the end of the clinical investigation.

14.2. Data protection

Coloplast protects all personal information and will only allow it to be used for the mentioned purposes related to only this investigation. Data will be stored in Rave EDC, version 2018.2.2, delivered by Medidata Solutions Inc. based in USA. The system is designed to be compliant with the FDA requirements of 21 CFR part 11.

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

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

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

14.3. Indemnity

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

[redacted]

[redacted]

14.4. Financial conditions

All financial agreements with the investigation sites involved in the clinical investigation will be specified in a sponsor investigator contract.

Coloplast A/S will compensate investigator and study nurses for their time and resources spent on the investigation (including overhead for the hospital and administrative costs) as specified in a sponsor investigator contract. [redacted]

Investigator has no apparent conflict of interest.

Subjects will be compensated with a voucher per visit with the value as described below:

[redacted]	Healthy volunteers
[redacted]	[redacted]

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

15. Adverse events, adverse device effects and device deficiencies

15.1. Adverse events

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

15.2. Adverse device effect

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

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

Table 2 lists anticipated ADEs that may occur.

ANTICIPATED ADES	INCIDENCE RATE
Urinary tract infection	Very unlikely
Macroscopic haematuria	Unlikely
Stinging and pain in urethra during catheterisation	Likely
Irritation of mucosa	Likely

Table 2 Anticipated ADEs and their likely incidence rates

15.3. 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.

15.4. Serious adverse events (SAE)

An SAE is an AE 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
    - a life-threatening illness or injury, or
    - a permanent impairment of a body structure or a body function including chronic diseases, or
    - in-patient or prolonged hospitalization, or
- 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 SAE 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 hospitalisation for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered an SAE.

15.4.1. Serious adverse device effect (SADE)

A serious adverse device effect (SADE) is an ADE that has resulted in any of the consequences characteristic of a SAE.

15.4.2. Anticipated serious adverse device effect (ASADE)

There are no anticipated SADEs.

15.4.3. Unanticipated serious adverse device effect (USADE)

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

15.5. Medical care of subjects

The principal investigator shall ensure that adequate medical care is provided to a subject experiencing an AE during and after participation in the clinical investigation. All SAEs will be followed until a resolution is addressed.

Subjects are informed to contact investigator if any AEs should occur during the investigation. Furthermore, 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 AEs is documented during site close-out.

15.6. Reporting and timelines

15.6.1. Investigator's reporting responsibilities

- The principal investigator at the site must assess all (S)AE`s that occur.

All SAEs 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 an SAE 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 ADEs 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 AE/SAE/device deficiency form.

Please report to [redacted]. In cases where accessing e-mail is not possible, please call Clinical Manager, [redacted]

15.6.2. Sponsor's reporting responsibilities

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

- All SAEs.
- All SADEs.
- All device deficiencies that could have led to SAEs 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 SAE 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 SAE, sponsor must immediately but no later than 2 calendar days after awareness by sponsor report the event to Danish regulatory authorities.

16. Suspension or premature termination of the clinical investigation

Sponsor may suspend or prematurely terminate the investigational 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 Ethical Committee. If monitoring or auditing of the clinical investigation identifies serious or repeated deviations at the participating site, sponsor will suspend or terminate the site. The sponsor or investigator will inform the regulatory authority as appropriate and notify the Ethical 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.

17. Clinical investigation report

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

Sponsor and principal investigator must sign the final version of the clinical investigation report or an affidavit, indicating their agreement with the contents. 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.

18. Publication policy

18.1. General

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

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

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