Clinical Investigation Plan

CP353

A randomized, open-labelled, crossover study confirming performance of a single-use intermittent micro-hole zone catheter in a population of adult male intermittent catheter users.

July – December 2022

Date: August 2, 2022

NCT05485922

CHANGE LOG

VERSION NUMBER	ISSUED BY *(INITIALS)*	COMMENTS (MAJOR CHANGES SINCE LAST REVISION)
1.0	[redacted]	First approved version

Exploratory endpoints:

- Pressure measurement at first flow-stop derived from a catheterisation profile, [mbar]
- Post-catheterization volume post catheterisation measured with a bladder scanner assessed by the average of 3 consecutive measurements [mL]

Population/subjects:

The clinical investigation will be conducted in 42 subjects enrolled in 1-3 clinical investigation sites in Denmark and USA.

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

Inclusion criteria	Exclusion criteria
1. Is Male	1. Is participating in any other clinical study during this investigation
2. Is at least 18 years of age and has full legal capacity	2. Has previous participated in this study
3. Has given written informed consent	3. Has symptoms of urinary tract infection as judged by the investigator
4. Has signed letter of authority (only DK)	4. Is an individual with history, suspected or showing signs of producing urine with excessive amount of mucus or large/clustered sediments or debris
5. Has used clean intermittent catheterisation CH12 or CH14 for at least one month	5. Has any known allergies towards ingredients in the investigational device
6. Use intermittent catheterisation as the primary bladder emptying method	
7. Is able (assessed by investigator) and willing to follow study procedures	

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4 Investigational device and comparator(s)

4.1 Description of investigational device

The investigational device is a ready-to-use, sterile, hydrophilic-coated male catheter for intermittent catheterisation. The device is for single use only and is intended to be used for drainage of the bladder through the urethra by people with missing or reduced bladder control.

The investigational device has a flexible tip (Flex tip) that facilitates passage through the sphincter in the urethra and is compositionally identical to the already CE-marked SpeediCath® Flex. The only difference is the design and manufacturing method of the drainage holes. [redacted]

The device is intended to be used by male catheter users in this clinical study.

The investigational device includes a coating system to reduce surface friction. A sleeve around the investigational device keeps the coating and catheter sterile through insertion.

The drainage end of the investigational device has an outlet to which a urine bag with a suitable connector can be connected. At the end of the sleeve there is a guide tip to help protect the user not to touch the catheter shaft and make it easier to insert the catheter.

The primary packaging provides the sterile barrier of the investigational device and contains tear opening as a proof of seal for identification of used devices. All legally required information is presented on the investigational device primary packaging.

The investigational devices are sterile by radiation.

The investigational devices are neither CE-marked in EU nor 510k-cleared in the US.

4.1.1 Manufacturing

Responsible for manufacturing the investigational device:

Coloplast A/S
Holtedam 1
3050 Humlebæk
Denmark.

4.2 Identification and traceability of the device

All investigational devices are labelled as per regulations and include "Exclusively for Clinical Investigational" on the label. The devices are also identified with study number, device name/code, and item/lot number and is accounted for through a master sponsor accountability log.

Figure 4-2 illustrates the labels for the investigational devices.

4.7 Description of the comparator product(s)

The comparator will be Hollister VaPro, a single-use hydrophilic sleeved soft/flexible catheters in the sizes CH12 (Item 72124) or CH14 (Item 72144). Hollister Vapro is CE-marked in EU and 510k-cleared in the US.

As the comparator devices are 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 14155:2020 and is thus not described into further details here.

Coloplast A/S will provide comparator devices to sites.

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

5 Design of the clinical investigation

5.1 General

The investigation is a multi-centre, randomised, controlled crossover study including 42 male IC users.

The total study duration for the individual subject will be between 3 days to 2 weeks, consisting of three site visits. Visits 0 is an information visit and can be combined with V1 if subjects prefer. For visit 1 and 2, one catheterization will be performed in the hospital setting by a health care professional assessing flow stop episodes, bladder emptying and haematuria. Visit 2 can be performed the day after visit 1, or maximum 14 days after visit 1.

The study design and procedures are described below in Figure 5-1.

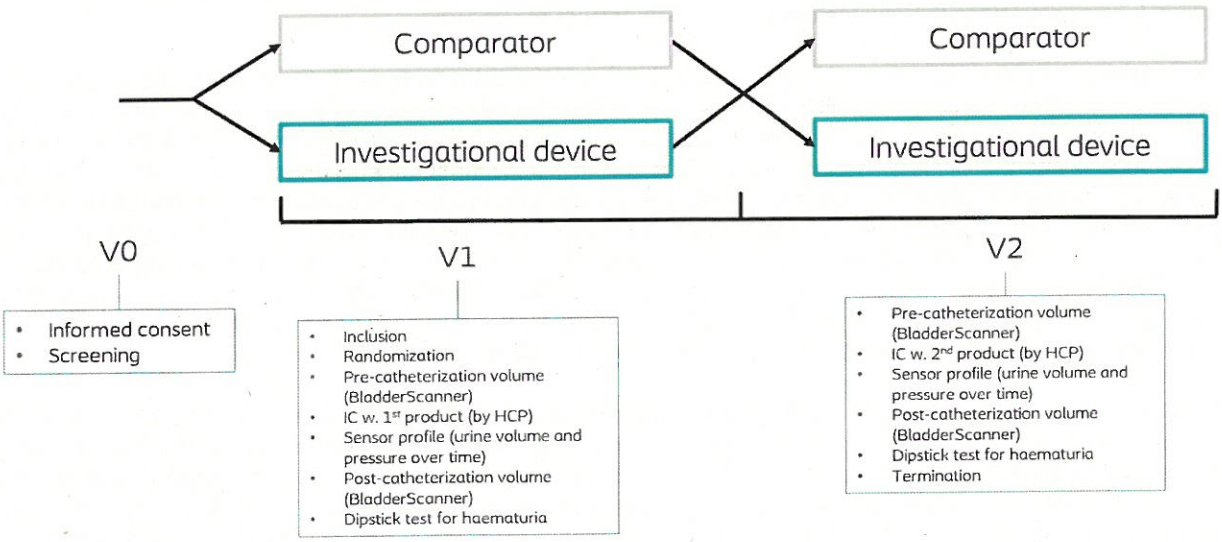

Figure 5-1 Study design

5.2 Primary endpoints

- Number of flow-stop episodes derived from a catheterisation profile, [number].
- Residual volume at 1st flow-stop i.e., post catheterisation volume minus volume at 1st flow-stop, both derived from a catheterisation profile, [g].

5.3 Exploratory endpoints

- Pressure measurement at first flow-stop derived from a catheterisation profile, [mbar]

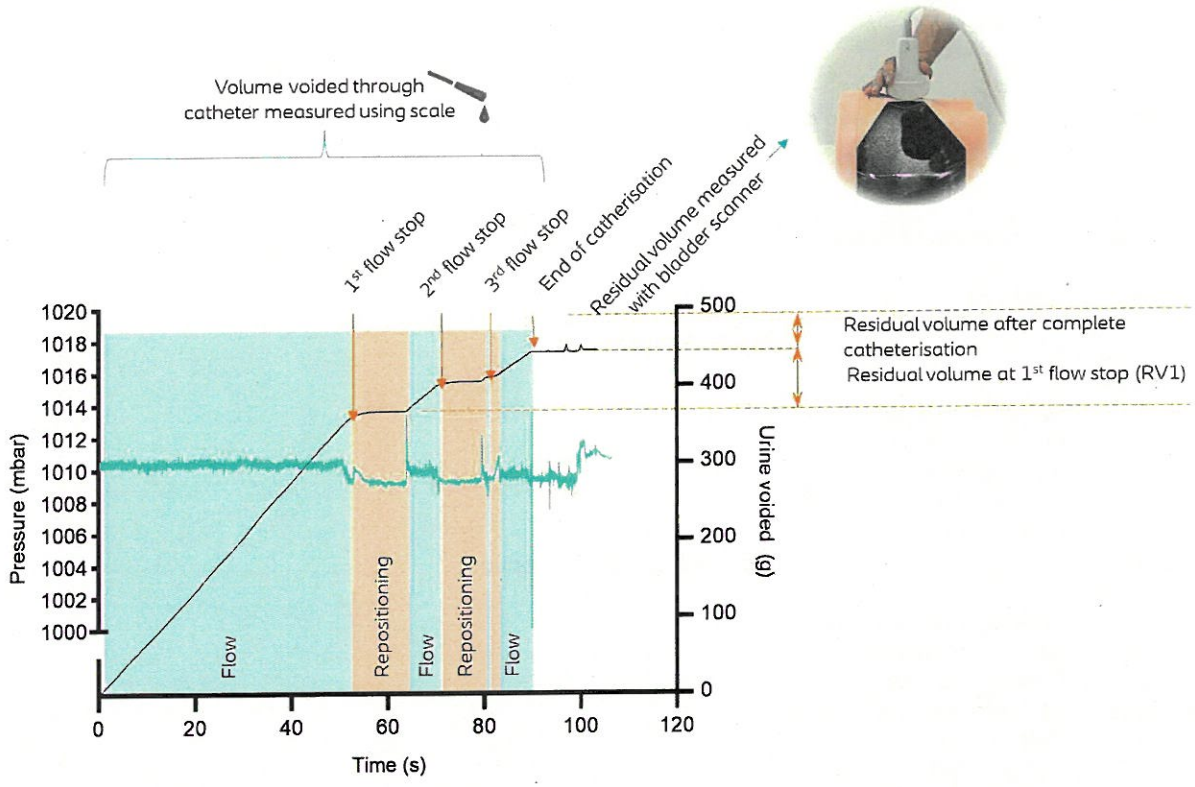

Figure 5-2 Overview of measurements during and after catheterisation.

Microtrauma: Concentration of microscopic haematuria and incidences of positive haematuria indicates possible catheter-associated microtrauma. With the micro-hole zone catheter, fewer mucosal suctions and putatively less or no co-sequential blood in the urine is expected. This is based on previous literature showing mucosal suction and associated trauma with indwelling catheters (Glahn, 1988; Glahn et al., 1988; Grocela & Jura, 2010; Milles, 1965), which has also been demonstrated with conventional 2-eyelet intermittent catheters in the preclinical setting (Coloplast A/S, 2021b, 2021c) (data not yet published).

5.6 Demography and potential compromising factors

The following baseline data will be collected and registered at visit 1(V1) by the investigator or designee:

- Date of informed consent
- Date of visit
- Age
- When did you start using a catheter? (months or years)
- Average number of catheters used per day during the last month
- Current device brand/type (can choose more than one)
    - Braun Actreen
    - Bard
    - Bullens
    - CliniMed
    - Coloplast
    - ConvaTec
    - Cure
    - HOllister
    - Manfred Sauer
    - TeleFlex
    - Wellspect
    - Oasis
    - LentisMed

- Second sequence: The comparator, then the investigational device.

Randomisation will be centralized using Medidata RAVE, see section 11.

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 IRB/EC and regulatory authorities will be notified.

First patient in (FPI)	July 2022
Last patient in (LPI)	October 2022
Last patient out (LPO)	October 2022
Database lock (DBL)	November 2022

6 Clinical Investigation population

The clinical investigation will be conducted in 42 subjects enrolled in 1-3 clinical investigation sites in Denmark and USA.

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

For a subject to be eligible, all inclusion criteria must be answered "yes":

Inclusion criteria	Justification for inclusion criteria
1. **Is Male**	Intended patient population of investigational and comparator devices.
2. **Is at least 18 years of age and has full legal capacity**	Intended patient population of investigational and comparator devices. To meet Helsinki Declaration.
3. **Has given written informed consent**	To ensure that the subject has been given written and oral information regarding the investigation and know enough about the investigation to decide on participation. To ensure voluntariness and that Helsinki Declaration is met.
4. **Has signed letter of authority (only DK)**	Letter of Authority is a demand from Danish Medicines Authorities.
5. **Has used clean intermittent catheterisation CH12 or CH14 for at least one month**	To ensure that the subject is used to catheterization.
6. **Use intermittent catheterisation as the primary bladder emptying method**	To ensure that the subject is used to catheterization.
7. **Is able (assessed by investigator) and willing to follow study procedures**	To ensure sufficient data for successful completion of the study.

6.1.2 Exclusion criteria

For an eligible subject, all exclusion criteria must be answered "no":

Exclusion criteria	Justification for exclusion criteria
1. **Is participating 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 relate to use of the herein tested devices. Also, to eliminate unintentional effect from other devices/medicines on the investigation's data.
2. **Has previous participated in this study**	To ensure integrity of results.
3. **Has symptoms of urinary tract infection as judged by the investigator**	To ensure subject safety and integrity of results.

'recruitment landing page'. CROs will assist by receiving 'reply to' letters/mails and/or answering the phone from interested subjects.

6.2.5 Coloplast database

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, male 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).

6.3 Subject withdrawal criteria

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

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

- Noncompliance with the CIP impacting the scientific integrity of the investigation.
- If subject's safety and wellbeing is compromised by further participation.
- Subjects lost to follow-up. At least three documented attempts will be made to verify subjects lost to follow-up.

Randomized subjects that for some reason withdraw from the clinical investigation can be replaced. Replacements should be discussed with Sponsor. Please also refer to section 10.2 Sample size for further information.

6.4 Point of enrolment

A subject is considered enrolled in the investigation at the time at which, following recruitment and before any clinical investigation-related procedures are undertaken, the subject signs and dates the informed consent form.

6.5 Subject Identification and Confidentiality

Subjects will be identified on the electronic CRF (eCRF) 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 eCRF are confidential and will only be available to the sponsor (including sponsor delegates), members of data management teams, the statistician, members of the EC or IRB 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 into the clinical investigation.

7 Procedures

7.1 Clinical investigation-related procedures

Visit 0 (V0) - Screening:

- Subject is informed about the study and screened for eligibility.

Visit 1 (V1):

- Informed consent obtained
- Check of inclusion and exclusion criteria

Concomitant medication potentially affecting urinary function (assessed by investigator)	Investigator/delegate		X	X
Relevant medical history	Investigator/delegate		X	
Randomization	Investigator/delegate		X	
Pre-catheterization volume measured 3 times with bladder scanner: - The test can only proceed after 3 consecutive measurements above 150 ml - If below 150 ml, subjects are required to drink at least 500 ml fluids for the next hour, and then measurements are retaken	Investigator/delegate		X	X
Registration/measurement of end points				
Catheterisation measuring sensor profile	Investigator/delegate		X	X
Urine volume at 1st flow stop	Investigator/delegate		X	X
Urine volume measured post catheterisation	Investigator/delegate		X	X
Post-catheterization residual volume measured 3 times with a bladder scanner	Investigator/delegate		X	X
Dipstick test for haematuria (post catheterisation)	Investigator/delegate		X	X
AEs/ADEs/SAEs/SADEs/DDs	Investigator/delegate		X	X
Termination form	Investigator/delegate			X

7.3 Case Report Forms

All assessments and observations throughout the investigation for each subject must be carefully recorded in an electronic CRF (eCRF).

CRFs will be filled in by the investigator and/or delegated site personal, who have signed the Site Personnel Signature and Delegation List and Clinical Investigation Training Log. The delegated site personal will be required to complete e-learning prior to system access. Delegated personal will receive credentials.

It is the responsibility of the Investigator that all data are entered promptly and correctly.

7.4 Concomitant treatment

Concomitant medication, potentially affecting urinary function (assessed by investigator), taken from the time of consent through the study, until termination will be registered in the eCRF in the concomitant medication section.

To the extent possible – the subjects should not have changed their medication the last 24 hours before visit 1 and 2. Any changes in medicine potentially affecting urinary function (assessed by investigator), should be recorded under concomitant medication.

event or serious adverse event (how, when, to whom), and who to contact in case of emergency related to the investigational device.

9 Monitoring Plan

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

The monitors will be the primary contact for the principal 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.

9.1.1 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 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.

9.1.2 Initiation visit

All clinical investigation sites will complete an initiation visit during which full training on all aspects of the clinical investigation will be provided.

Training in use of the equipment used for measuring endpoints will be performed at sites.

9.1.3 Monitoring visit(s)

The sponsor shall determine the extent and nature of monitoring appropriate for the clinical investigation based on the risk assessment. The sponsor shall ensure, through oversight of the clinical investigation and timely adverse event reporting, that unanticipated adverse device effects are identified and investigated rapidly so that, where necessary, additional risk control measures can be implemented.

The site dedicated monitor is to ensure adherence to the clinical investigation plan, the safety of the subjects, accurate data recording on the e-CRFs and to monitor recruitment rates and adherence to follow-up schedules. During the clinical investigation, monitors shall check that appropriate written informed consents have been obtained. The Principal 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 period of involvement for each clinical site personnel must be documented on the Site Personnel signature and Delegation list as well as training received before getting involved with the clinical investigation must be documented in the Clinical Investigation Training Log.

The monitor shall inform the sponsor about any problems relating to facilities, technical equipment or medical staff at the clinical investigation site. The monitor shall also be responsible for notifying such deficiencies in writing to the principal investigator and convene with the clinical investigation site personnel appropriate and timely corrective actions.

The sponsor, or delegate, will provide clinical monitoring, including review of eCRF with verification to the source documentation.

The monitor shall make written reports to the sponsor, including documentation of any deviations after each visit and provide written follow up action items if any, to the principal investigator and/or clinical investigation site personnel.

Baseline assessments and endpoints will be reported by descriptive statistics and/or listed. Summaries will be presented by device i.e., investigational or comparator device 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.

All statistical analysis will be performed with SAS (version 6.4/Enterprise Guide version 7.1).

10.2 Definition of analysis populations

Screening Failures (SF), Intention to Treat (ITT), Full Analysis Set (FAS), Safety and Per Protocol (PP) analysis set will be defined at a formal data review meeting prior to database lock. As a minimum, the data manager, the clinical manager, and the statistician will be involved in the classification of subjects.

Subjects not adhering to inclusion and/or exclusion criteria are considered screening failures (SF) and are not randomised.

The Safety population will constitute all subjects enrolled i.e., subjects who have given informed consent.

The ITT population will constitute all randomised subjects.

The full analysis set is a modified ITT population i.e., a sub-population of the ITT population, and will constitute all randomised subjects, who have been exposed to at least one device, with at least one endpoint recorded (data non-missing).

The PP is a sub-population of the full analysis set where all subjects have received treatment as per protocol.

Individual endpoints/data points may be excluded from the analysis, even though the corresponding subject belongs to any of the pre-defined populations. Exclusion of subjects or data points must be documented.

All statistical analysis and test of hypothesis will be based on the full analysis set, and in addition, Primary and Secondary endpoints will also be analysed in the PP population, if the PP population differs from the full analysis set. whereas adverse events and device deficiencies will be assessed in the safety population.

10.3 Multiplicity control and adjustment of error probabilities

The family-wise Type I error rate will be controlled in a hierarchical fashion in support of demonstrating superiority of the investigational device.

The primary endpoints will be evaluated in a fixed sequence, where the first null-hypothesis must be rejected at a 5% significance level (alpha 0.05) before proceeding with the next.

10.4 Analysis of the primary endpoints

- Residual volume at first flow-stop, will be analysed in a general linear mixed model with subject included as a random component. Evidence of superior effect will be concluded, if the 95% confidence interval of the difference between comparator and investigational device, do not include zero.

- Number of flow-stop episodes will be analysed, in a generalized linier mixed model, with subject included as a random component. Evidence of superior effect will be concluded, if the lower 95% confidence limit of the risk ratio between comparator and investigational device, is more than 1.

The models will include following fixed effects.

- Visit (visit 1 and 2 of catheterisation)
- Device (comparator and investigational device)

The power for concluding superiority of the investigational device is at least 90% or higher.

11.2 Pass/fail criteria

To demonstrate superiority of the investigational device, the null hypothesis of the primary endpoints must be rejected, at a 5% significance (alpha 0.05).

The pass criteria for the study are based on the results from analysing the two primary endpoints in a hierarchical fashion: rejecting the null-hypothesis on the first endpoint (Residual urine at first flow-stop) before continuing to the second (Number of flow-stop episodes).

12 Data management

12.1 Data collection and data management

12.1.1 Data Collection in the clinical investigation

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

Data will be collected through an electronic data capturing (EDC) system on electronic Case Report Forms (eCRF), a secure, internet-based case report form. 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 2021.2.1, 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 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 reviews (according to the source data specification form). The eCRF will be completed on a continuous basis starting from the point of enrolling the subject to final follow up.

The eCRF will be completed by the investigator, or delegate, who have signed the Site Personnel Signature and Delegation List and Clinical Investigation Training Log. It will be the responsibility of the investigator to ensure that all measurements and observations are correctly noted in the eCRF.

All assessments and observations throughout the investigation for each subject must be carefully recorded in an eCRF during the visit or immediately after. The eCRF makes it possible to enter data right away when they are obtained. This is the preferred way of collecting data. In case this is not possible the data should be entered no later than 5 days after the visit / procedure.

Adverse events should be registered following the timelines described in the Adverse Event section.

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

Raw data from the pressure sensor are stored in the electric boxes and copied on USB sticks. The USB sticks are sent to Coloplast A/S via courier. Raw data from either the USB sticks or the electric box are then analysed by two specialists independently.

A calibration/comparison is then performed between the two specialists and an excel sheet is made combining the relevant data. The excel sheet is thereby uploaded to an allocated SharePoint. Hereafter, the data derived from the catheterisation profile will be batch uploaded into the EDC system.

The site will complete a deviation eCRF form for all data-related deviations and all deviations that are not related to the data (for example, an untrained nurse performing study procedures) are reported by the monitor in the Site Report – Periodic Monitoring and actions are addressed to the Investigator for completion.

If any deviations to the investigation plan are detected during the monitoring visit, the Monitor shall ensure the site reports all deviations in the eCRF or on the Deviation log in the Investigator File. Additionally, the monitor must report any deviation noted during the visit in the Periodic Monitoring Report.

Monitor will align with data management in each investigation, how data management will be informed about all deviations.

The following information about the deviation will be collected:

- Site ID
- Subject ID
- Date the deviation took place
- What the deviation is related to
- If the deviation affects data integrity
- If the deviation affects subject safety
- Supplementary description of the deviation
- Actions taken with regards to the deviation

15 Device Accountability

All access to the investigational devices (including comparators) 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 investigations devices to the investigational sites until return of or disposal.

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

- Date of receipt.
- Identification of each investigational device (batch no./serial no./unique code).
- The expire date,
- The date(s) of use.
- Subject identification.
- The date on which the investigational device was returned/explanted from the subject

The date of return unused, expired or malfunctioning investigational devices

16 Statement of compliance

The clinical investigation is conducted in accordance with:

- Ethical principles that have their origin in the Declaration of Helsinki, 1964, Last amended at the 59th WMA General Assembly, Brazil, October 2013.
- MDR (EU) 2017/745
- ISO 14155:2020 **"Clinical Investigation of medical devices for human subjects** – Good clinical practices".
- Any applicable regional or national regulations will be specified in the country specific CIP.

16.1 Ethics committee, Institutional Review Board and regulatory authorities

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

[redacted]

16.4 Financial conditions

Coloplast A/S will compensate all 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 agreement.

17 Informed consent process

Written informed consent is obtained from all subjects participating in the investigation after thorough written and verbal information. The information is given by the investigator or his/her representative **in the subjects'** native non-technical language. Each subject will be fully informed about the aim of the investigation, procedures, potential risks or inconveniences and/or expected benefits, all anticipated adverse device effects and then have a minimum of 24h (ensure ample time) 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 PI or his/her representative responsible for conducting the informed consent process. A copy will be provided to the subject.

If new information is to be given during the investigation, sponsor will inform the investigators, and the new information is given to the subjects by the investigator. If new information becomes available that can **significantly affect a subject's future health and medical care that information will be provided to the subject** in written form. CM is responsible for writing the information and providing the approved Subject Information and Consent Form to investigators that will further provide it to the subjects. If applicable, all affected subjects shall be asked to confirm their continuing informed consent in writing.

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

18 Subject compensation

18.1 Compensation in case of injury

Product liability and No-Fault Clinical Investigation Insurance covering the duration of the clinical investigation are in place, to enable compensation in the event of an injury to a participating subject.

18.2 Compensation for participating in the clinical investigation

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

	Subjects
Visit 0 (V0)	-
Visit 1 (V1)	[redacted]
Visit 2 (V2)	[redacted]

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

19 Adverse events, adverse device effects and device deficiencies

19.1 Adverse events

An adverse event is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, whether or not related to the investigational medical device(s) or the comparator(s), or the procedures involved. The adverse event shall be marked with the intensity mild, moderate or severe. This could include events such as headache or dizziness.

19.4.3 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.

19.5 Medical care of subjects

Principal investigator shall ensure that adequate medical care is provided, during and after participation in the clinical investigation, to a subject experiencing an adverse event. All ongoing ADEs, SAEs, SADEs and DDs that could have led to a SAE at subject termination will be followed according to the Risk Benefit analysis (see 8.2). An ongoing adverse event at subject termination visit is documented as the current status for the adverse event and will not be followed up.

The subjects shall be informed of any new significant findings occurring during the clinical investigation, including the need for additional medical care that can be required, and of the nature and possible cause of any adverse events experienced.

19.6 Reporting and timelines

19.7 Investigator's reporting responsibilities

- PI at each site must assess all (S)AE`s that occur at his/her site.

- All serious adverse events and serious adverse device effects must be reported to sponsor within 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 related to investigational product and/or comparator must be reported to sponsor within 24 hours 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.
- **Possible 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.
- **Probable 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.

and the intensity of the event should be considered, as such:

- **Mild,** the intensity of the event is mild with no further action or intervention
- **Moderate,** the intensity of the event will lead to an action or intervention to solve the event
- **Severe,** the intensity of the event will lead to follow up on the action or intervention, as the effect of the action or intervention may not decrease the symptoms.

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

The investigation will be registered in a publicly accessible database before recruitment of the first subject. The results of the investigation, positive as well as inconclusive and negative will be published in the same 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.

23 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.

24 Bibliography

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