Clinical Investigation Plan

CP327

Randomized clinical trial assessing the effect of transanal irrigation with cone catheter versus conservative bowel management on symptoms of low anterior resection syndrome after rectal resection

January 2020- Maj 2021

21st of January 2020

Study Sponsor / Data Controller: Coloplast A/S

Holtedam 1

3050 Humlebæk

Denmark

NCT04586634

[redacted]

SYNOPSIS OF THE CLINICAL INVESTIGATION

Synopsis of the clinical investigation

Objective

The primary objective is to demonstrate superiority of the Peristeen cone catheter compared to standard of care.

The secondary objective is to investigate quality of life and different benefits and aspects of treatment and satisfaction with the Peristeen cone catheter.

Design of the investigation

This is a randomised, open-label, parallel investigation comparing the Peristeen cone catheter with standard of care in subjects with major LARS (LARS score ≥ 30). Each subject will be enrolled for a study duration of 12 weeks. Subjects will be randomized to the treatments stratified by neo-adjuvant radiotherapy.

The comparator in this study will be current standard of care for patients with LARS which is conservative bowel management. This is defined as: Supportive therapy according to the individual treatment protocols available at each participating site.

Primary endpoint and secondary endpoints

Primary endpoint:

- LARS score, obtained from the LARS score questionnaire*

Secondary endpoints:

- Number of subjects with Major LARS*
- FIQL Score – scale 1, Modified American Society for Colorectal Surgeons Questionnaire*
- FIQL Score – scale 2, Modified American Society for Colorectal Surgeons Questionnaire*
- FIQL Score – scale 3, Modified American Society for Colorectal Surgeons Questionnaire*
- FIQL Score – scale 4, Modified American Society for Colorectal Surgeons Questionnaire*
- EQ-5D-5L – utility score*
- EQ-5D-5L – VAS score (scale 0-10 cm)*
- Satisfaction with treatment (scale 0-10 cm)*
- Number of adverse events*

*All endpoints are measured per subject at study termination

Exploratory endpoints:

- [redacted]

*All endpoints are measured per subject at study termination

[redacted]

9. Postoperative radiotherapy for rectal cancer	Can potentially affect LARS
10. Underlying diarrhoeal disease	Can potentially affect LARS
11. Neurologic disease assessed to be a significant contributory cause to LARS symptoms	Can potentially affect LARS
12. Former or current use of transanal irrigation	Patients to be naïve to transanal irrigation
13. Participating in other interventional clinical investigations	Can potentially affect LARS

Investigational devices and comparator

The Peristeen transanal irrigation system is a manual system consisting of a control unit (featuring a pneumatic bulb pump and a four-position rotary switch), a water bag (featuring a pressure relief valve), a cone catheter, tubes and connectors. The system is also accompanied by straps to secure the system on the thigh while being used, if needed, and a toilet bag to store the system in when not in use. Peristeen is a non-sterile product classified as class I device according to the Medical Device Directive, MDD 93/42/EEC and is CE-marked.

The comparator in this investigation is current standard of care for patients with LARS which is conservative bowel management.

Investigation approval

The investigation will be approved by the Ethical Committee in France and notified to French ANSM and French Data Protection Body (named CNIL) when receiving the EC approval, before the investigation can be initiated.

[redacted]

Assessment(s)						
On-site visit • LARS score Questionnaire • FIQL score Questionnaire • EQ – 5D – 5L • Satisfaction with treatment • [redacted] •	Subject/Investigator (All)		X			X
On-site visit • [redacted] •	Subject/Investigator (Peristeen Cone only)					X
Subject diary: • [redacted] •	Subject (All) Run-in period (14 days from Visit 1)		X	X		
Subject diary: • [redacted]	Subject (Peristeen Cone only)			X		
Device training	Investigator		X			
AE/SAE reporting			X		X	X
Registration of termination						
Termination form	Investigator					X

[redacted]

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[redacted]

[redacted]

features a balloon catheter, that stays in the bowel during irrigation creating a seal, and was especially developed with the neurogenic patients in mind (e.g. Spinal Cord Injury, multiple sclerosis and spina bifida), addressing their particular needs, e.g. reduced hand dexterity and an altered or absent sphincter tone.

The newly developed and CE-marked device Peristeen Cone catheter has been designed to be better suited for patients with specific clinical and anatomical considerations such as LARS patients in view of their post-surgical bowel anatomy. Furthermore, due to sphincter-sparing surgical techniques, the majority of LARS patients have an acceptable sphincter function and good hand dexterity, thus limiting the need for a self-supported inflatable balloon catheter.

The current standard of care for patients with LARS is conservative bowel management. This is defined as supportive therapy according to the individual treatment protocols available at the site. However, many patients continue to suffer from LARS symptoms despite the conservative bowel management. The objective of the study is therefore to demonstrate that the Peristeen system with Cone Catheter is superior compared to standard of care for patients with LARS symptoms.

3. Objective of the clinical investigation

3.1. Objective

The primary objective is to demonstrate superiority of the Peristeen cone catheter compared to standard of care.

The secondary objective is to investigate quality of life and different benefits and aspects of treatment and satisfaction with the Peristeen cone catheter.

4. Investigational device and comparator(s)

4.1. Description of investigational device

The Peristeen transanal irrigation system is a manual system consisting of a control unit (featuring a pneumatic bulb pump and a four-position rotary switch), a water bag (featuring a pressure relief valve), a lubricated cone catheter, tubes and connectors. The system is also accompanied by straps to secure the system on the thigh while being used, if needed, and a toilet bag to store the system in when not in use. Peristeen is a non-sterile product classified as class I device according to the Medical Device Directive, MDD 93/42/EEC and is CE-marked.

[redacted]

4.7. Comparator

The comparator in this investigation is current standard of care for patients with LARS which is conservative bowel management. This is defined as supportive therapy according to the individual treatment protocols available at each participating site.

For LARS patients these protocols consist of:

- Dietary modifications (bulk forming)
- Biofeedback-assisted pelvic floor training
- Abdominal massage
- Treatment with loperamide, oral laxative and suppositories
- Digital rectal stimulation
- Small volume enemas (< 150 ml)

5. Design of the clinical investigation

5.1. General

This investigation is a randomised, open-label, comparative, parallel, post market study. In total, 34 rectal resection subjects with major LARS will be included and randomised, and each subject will have an inclusion visit and two test visits and follow-up phone calls in between. Each subject will be enrolled for a study duration of 12 weeks. Subjects will be randomized to the treatments stratified by neo-adjuvant radiotherapy. Training will be performed at the randomisation visit V1. If needed, patients may have additional training sessions before being able to perform the irrigation on their own. After the training sessions the study duration is 12 weeks.

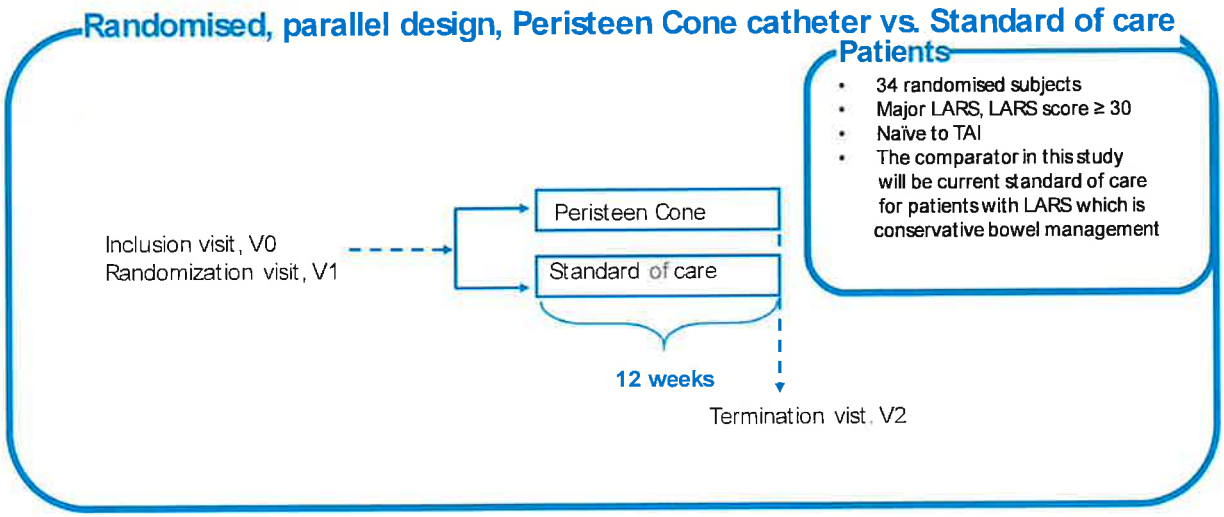

Figure 1 Design of the randomised clinical study

5.2. Primary endpoint

- LARS score, obtained from the LARS score questionnaire* (6)

5.3. Secondary endpoints

- Number of subjects with Major LARS*
- FIQL Score – scale 1, Modified American Society for Colorectal Surgeons Questionnaire* (7)

[redacted]

5.7. Randomisation Procedure

As this is a parallel investigation, subjects are assigned to one treatment in a 1:1 allocation ratio, where each subject will be randomized into one of two treatment arms i.e. investigational device and comparator.

At visit 1 investigator or his representative, as per the randomisation list, allocates a randomisation treatment code to each patient. The randomisation code is recorded in the electronic Case Report Form (eCRF) by investigator or his representative.

5.8. Blinding

Subjects will not be blinded in this investigation due to self-management of the investigational device. Furthermore, site personnel i.e. nurses and/or assisting Coloplast personnel are also not blinded. Coloplast personnel not on-site or involved in trial conduct i.e. the statistician will be blinded until the time of data base lock.

As this is a parallel study, subjects will be assigned one treatment only and randomly assigned a treatment in a 1:1 allocation ratio for the duration of the study.

5.9. Total expected duration of the clinical investigation

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

Activity	Estimated time
First subject enrolled	SEP 2020
Last subject enrolled	FEB 2021
Last subject completed	MAY 2021
Final Report	AUG 2021

6. Clinical Investigation population

The clinical investigation will be conducted in 34 subjects enrolled in 4-8 clinical investigation sites.

Patients who have undergone rectal resection for rectal cancer (with or without pouch construction) and have major LARS defined as LARS score ≥ 30.

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

Table 1 Inclusion criteria and justification hereof:

Inclusion criteria ***To be included the subjects must:***	**Justification** ***To ensure that:***
1. Be at least 18 years of age and have full legal Capacity	To ensure voluntarily and that the Helsinki declaration is met
2. Have given written informed consent	To meet the Helsinki declaration

[redacted]

6.1.3. Pregnancy

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, to ensure the subject is not pregnant. The urine pregnancy test will be performed by dipstick at the trial site. Furthermore, the female patients with childbearing potential should use safe contraceptives during study duration.

6.2. Recruitment and enrolment

Recruitment of potential subjects will begin once all regulatory requirements have been fulfilled. The recruitment time is estimate to approximately 6 months.

Recruitment method	**Coloplast Database**
Potential subjects	Recruitment will go through the Investigators own patient database Potential subjects are identified by the following searching criteria: • Have a LARS score ≥ 30 after rectal resection • Patients must be evaluated to be suitable for transanal Irrigation procedure with a cone catheter by endoscopy, defecography or comparable procedure • Be at least 18 years of age
First contact	The identified potential subjects will as first contact be sent an Invitation and Reply Letter by mail or email. If a potential subject does not return the reply letter or answer the email, they may be contacted by phone, mail or email to make sure that they have received the approach.
Second contact	If potential subjects return the Reply Letter/reply to the email or have called the investigator as first contact and are interested, the Investigator or delegated site personnel will contact the subjects by phone and give a short introduction to the investigation and go over the inclusion and exclusion criteria. If the subjects do not meet the inclusion criteria or meet the exclusion criteria, this will be registered in the Subject Screening Log.
Subject Information Form	If subjects are eligible and interested in participating, then written information about the investigation (subject information) will be sent to the subjects to ensure that they are given the opportunity to read about the investigation before a possible informational visit, and so that they can prepare any possible questions they may have. Information visit V0 will be booked at this point and the subjects are instructed to contact the investigator or delegated study personnel if they, after having read the subject information, no longer are interested in participation in the study.
First visit Information visit	If an eligible subject is interested in participating, baseline visit (V0) will be arranged. When arranging the visit, it will be ensured, that the subject has received 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. See section 16. for information to be given to the subjects, as well as the informed consent process.
Enrolment and Baseline visit (V0)	The subjects will be offered at least 24 hours to think about if they will participate, or if they wish to give consent right away. If/when the subject decides to participate, he/she will be asked to sign the relevant forms (see section 16). If a subject so desires, and it is certain that it is understood what the investigation entails, and the relevant forms have been signed the subjects are considered enrolled in the investigation.

[redacted]

- Instruct subject in completing subject diaries
- Instruct subject in use of the investigational devices/standard of care
- Instruct and remind the subject to follow the study specific procedures between visits
- Schedule next visit in 12 weeks

Phone call (twice a week for the first 3 weeks; 6 phone calls, 30 mins):

- Give support in the use of the investigational device/standard of care
- Remind the subject to complete diaries
- Complete eCRF
- Registration of AEs/ADEs/SAEs/SADEs
- Remind the subject to follow the study specific procedures between visits

Termination visit (V2) after 12 weeks (± 4 days):

- Complete eCRF
- Complete QoL questionnaires
- Registration of AEs/ADEs/SAEs/SADEs
- Review AEs/ADEs/SAEs/SADEs
- Collect subject diaries
- Collect investigational device
- Fill in termination form

[redacted]

Assessment(s)						
On-site visit • LARS score Questionnaire • FIQL score Questionnaire • EQ – 5D – 5L • Satisfaction with treatment • [redacted]	Subject/Investigator (All)		X			X
On-site visit • [redacted]	Subject/Investigator (Peristeen Cone only)					X
Subject diary: • [redacted]	Subject (All) Run-in period (14 days from Visit 1)		X	X		
Subject diary: • [redacted]	Subject (Peristeen Cone only)			X		
Device training	Investigator		X			
AE/SAE reporting			X		X	X
Registration of termination						
Termination form	Investigator					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) on a PC provided to the site by Coloplast.

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. As eCRFs are used delegated site personal will be required to complete e-learning prior to system access. Delegated personal will receive credentials.

Lars score, [redacted] questionnaire (FIQL and EQ-5D) will be filled out by subjects using paper CRF and entered into the eCRF afterwards.

[redacted]

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, a 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, or if it is not at all feasible to perform a Site selection visit on-site.

9.1.2. Initiation visit

All clinical investigation sites will get an on-site initiation visit during which full training on all aspects of the clinical investigation and the investigational device will be provided.

9.1.3. Monitoring visits

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

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

The monitor shall inform the sponsor about any problems relating to facilities, technical equipment or medical staff at the clinical investigation site. During the clinical investigation, monitors shall check that appropriate written informed consents have been obtained. 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.

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.

The monitor shall make written reports to the sponsor, after each visit and provide written action items if any, to the principal investigator or clinical investigation site personnel.
The first monitoring visit at the site should be conducted as soon as reasonably possible after the first subject(s) has(have) completed the first visit of the investigation. This is to minimise systematic errors done by site and to clarify potential questions before proceeding with enrolment of more subjects.

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

The monitor 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.

[redacted]

10.3. LARS score and Quality of Life questionnaires

LARS score questionnaire

Item values (5 items) will for each subject, be summarised to a LARS score with a LARS interpretation as stated below.

Interpretation:

0-20:	No LARS
21-29:	Minor LARS
30-42:	Major LARS

Symptom-related Quality of Life questionnaire (modified FIQL)

The FIQL scale is thus interpreted for four scales exploring different aspects of the patient's quality-of-life:

- Lifestyle (10 items) 2A, 2B, 2C, 2D, 2E, 2G, 2H, 3B, 3L, 3M
- Coping/behavior (9 items) 2F, 2I, 2J, 2K, 2M, 3C, 3H, 3J, 3N
- Depression/self-perception (7 items) 1, 3D, 3F, 3G, 3I, 3K, 4
- Embarrassment (3 items) 2L, 3A, 3E

The quality-of-life score is analysed for each scale. There is not a global score.

Items are scored 1 (lease satisfactory quality-of-life) to 4 (most satisfactory quality-of-life). Specifically, prior to estimating the Depression/self-perception scale, in question no. 1, "Excellent"/"Excellente" must be scored 5 and "Poor"/"Mauvaise" must be scored 1 (11).

The score for each scale is calculated by dividing the sum of the item scores by the number of items.

If data is missing for a given item, it is assigned a value equal to the average of the other items in the scale. If data are missing for half or more than half of the items, the scale cannot be interpreted.

EQ-5D-5L questionnaire

There should be only ONE response for each dimension. Missing values are preferably coded as '9'. Ambiguous values (e.g. two boxes are ticked for a single dimension) should be treated as missing values.

Each of the five dimensions comprising the EQ-5D descriptive system (mobility, self-care, usual activates, pain/discomfort, anxiety/depression) is divided into five levels:

- LEVEL 1: indicating no problem
- LEVEL 2: indicating slight problems
- LEVEL 3: indicating moderate problems
- LEVEL 4: indicating severe problems
- LEVEL 5: indicating unable to/extreme problems

A unique health state is defined by combining one level from each of the five dimensions. i.e. state 12345 indicates no problems with mobility, slight problems with washing or dressing, moderate problems with doing usual activities, severe pain or discomfort and extreme anxiety or depression, while state 11111 indicates no problems on any of the five dimensions.

Following endpoints ([redacted]):

[redacted]

Following endpoints (proportions):

- Number of subjects with Major LARS (≥30)

Will be analyzed, by a non-parametric chi-square test using proc FREQ in SAS. A test of H0 (no association) will be performed.

Following endpoints [redacted]

- [redacted]
- [redacted]

[redacted]

Following endpoints:

- The number of adverse events
- [redacted]
- [redacted]

Will be reported by descriptive statistics

Data obtained from the diary includes a run-in period of 14 day starting from visit 1. Analysis and descriptive statistics pertaining to diary data will not include the run-in period.

10.6. Sample size

The purpose of the study is to demonstrate superiority of the test product in the primary endpoint.

A sample size of 34 subjects (26 completers), assuming a drop-out rate of approximately 20%, gives sufficient power to demonstrate superiority of the test product. See **Table 4** and **Figure 2** for graphical presentation of the power and sample size, under varying values of mean difference.

Table 4 Power and sample size

[redacted]

minimal mean difference in LARS score of 7 between treatments (Peristeen cone and standard of care) is deemed clinically relevant.

The assumption of SD=6, is based on data provided by Martellucci et al., 2018 (13). Hence, the effective number of subjects needed to obtain approximately 80% power is 13 per group (17 subjects assuming a 20% drop-out rate).

10.8. Pass/fail criteria

The success criterion is to demonstrate superiority of the Peristeen Cone device in the primary endpoint.

10.9. Interim analysis

No interim analysis is planned for this study.

10.9. Statistical reason for termination of investigation

There is no reason to terminate the investigational study based on statistical considerations.

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

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

11. Data management

11.1. Data Collection in the clinical investigation

Data management and the final statistical analyses of all measurements described in this protocol are carried out by the [redacted] Coloplast A/S.

Data will be collected through an electronic data capturing (EDC) system on electronic Case Report Form (eCRF), a secure, internet-based case report form and on paper CRF for QoL questionnaires and subject diaries and entered into the electronic data capturing system. 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 [redacted] delivered by [redacted]. 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 and pCRF.

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.

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

[redacted]

- Monitor data quality through routine review of submitted data in real-time to identify missing data, inconsistent data, data outliers, and potential protocol deviations that may be indicative of systemic and/or significant errors in data collection and reporting at the site
- Verify source data remotely, provided that both source data and CRFs can be accessed remotely
- Conduct aggregate statistical analyses of study data to identify subject data that are outliers relative to others and to evaluate individual subject data for plausibility and completeness
- Conduct analyses of site characteristics, performance metrics (e.g., high screen failure rates, high frequency of eligibility violations, and delays in reporting data), and clinical data to identify early on corrective actions needed for characteristics correlated with poor performance or noncompliance

11.3. Data retention

The Investigator file must be archived for a minimum period of 15 years after the final clinical investigation report has been signed.

All investigation site documents must be archived for a minimum period of 15 years after the final clinical investigation report has been signed. The monitor is responsible for informing the investigator and the CM if this period should be longer for their sites according to local regulation.

12. Amendments to the Clinical Investigation Plan

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

All significant changes require notification to the EC and applicable regulatory authority. Substantial changes may require approval from the EC and applicable regulatory authority prior to implementation.

13. Deviations from the Clinical Investigation Plan

Deviations to the Clinical Investigation Plan occurs when the activities during the clinical investigation do not comply with the EC approved investigation plan. A minor deviation is defined as those that don't increase risk or decrease benefit or don't have a significant effect on the subject's rights, safety or welfare; and/or on the integrity of the data.

The investigator is not allowed to deviate from the Clinical Investigation Plan unless, under emergency circumstances or to protect the rights, safety and welfare of the subject(s).

For the purposes of this investigation, any variance from the protocol is considered a deviation and is to be reported.

The site will complete a deviation eCRF 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 in the Deviation Log located in the Investigator File.

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 (site ID), Subject (subject ID)

15.2. Data protection

As part of the investigation Coloplast A/S, Holtedam 1, 3050 Humlebaek, Denmark ("Coloplast") will collect and process the personal information the subject provides for the investigation ("subject personal data"). This includes identification and contact information (which may be pseudonymised) as well as information about product usage experience and your health. Coloplast will only process the subject's personal data:

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

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

Subject personal data will be kept as long as required under applicable laws and regulations. The EU Medical Device Regulation obligates Coloplast to keep the data for a period of at least 15 years after the investigation is completed, or, in the event that the device is subsequently placed on the market, at least ten years after the last device has been placed on the market. Subject personal data will be deleted at the end of the mandatory retention period.

If the subject has questions or queries regarding Coloplast's handling of personal information, the subject can always contact Coloplast's Data Protection Officer at [redacted]. Complaints related to Coloplast's handling of subject personal information may similarly be sent to the Data Protection Officer, and the subject are also entitled to file a complaint with the relevant supervisory authority, which in the case of France is the French Data Protection Agency: CNIL (*https://www.cnil.fr/fr/plaintes*).

The subject can write to [redacted] any time to request:

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

15.3. Indemnity

The Sponsor, Coloplast A/S, will maintain the appropriate and necessary insurance coverage for the duration of the study to cover costs incurred as a direct result of participation in the study.

15.4. 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 contract.

[redacted]

Cramps	>2 to ≤20 ppm
Mucosal tear	>0.02 to ≤0.2 ppm
Fissure	>0.02 to ≤0.2 ppm
Rectal bleeding	>0.2 to ≤2 ppm
Bowel Perforation	>0.02 to ≤0.2 ppm

18.3. 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.

Examples of device deficiencies are:

- Leakage between parts of the system (tubes, connector, water bag and control unit)
- pressure valve falling off
- functionality issues between connector and tube

18.4. Serious adverse events (SAE)

A serious adverse event is an adverse event that:

- Led to death,
- Led to a serious deterioration in the health of the subject, users or other persons as defined by one or more of the following:
  1) a life-threatening illness or injury, or
  2) a permanent impairment of a body structure or a body function including chronic diseases, or
  3) in-patient or prolonged hospitalization, or
  4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
- Led to fetal distress, fetal death or a congenital abnormality or birth defect.

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

18.4.1. Serious adverse device effect (SADE)

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

18.4.2. Anticipated serious adverse device effect (ASADE)

Anticipated serious adverse device effect is any event that by its nature, incidence, severity or outcome has been previously identified in the risk analysis report.

18.4.3. 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.

18.5. Medical care of subjects

Principal investigator shall ensure that adequate medical care is provided to a subject experiencing an adverse event during and after participation in the clinical investigation. All serious adverse events will be followed until a resolution is addressed.

inform the regulatory authorities and relevant EC(s). If monitoring or auditing of the clinical investigation identifies serious or repeated deviations at one of the participating investigation sites, sponsor will suspend or terminate the particular investigation site. The sponsor or investigator will inform the regulatory authority as appropriate and notify the EC about the termination of the site.

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

20. Clinical investigation report

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

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

The clinical investigation report must be submitted to EC and regulatory authorities.

21. Publication policy

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

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

22. 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.

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Signature Page for [redacted]

Approved	[redacted]
Approved	[redacted]
Approved	[redacted]

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