CLINICAL INVESTIGATION PLAN

A Prospective Nonrandomized Study of Autologous Muscle Derived Cell (AMDC) Transplantation for Treatment of Fecal Incontinence

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Sponsor and Manufacturer: Cook MyoSite, Incorporated
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CLINICAL INVESTIGATION PLAN SIGNATURE PAGE

This clinical trial will be conducted in compliance with the clinical investigation plan, GCP, and other applicable requirements as appropriate.

Signatures:
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CLINICAL INVESTIGATION PLAN SIGNATURE PAGE, CON'T

Principal Clinical Investigator

I hereby confirm that I approve of this Clinical Investigation Plan and agree to comply with its terms as laid out in this document.

Signature	DD/MM/YYYY
Printed Name	Title

CONFIDENTIALITY STATEMENT

This document shall be treated as a confidential document for the sole information and use of the clinical investigation team and the Research Ethics Board / Ethics Committee.

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1.0 Clinical Investigation Plan Overview

This study is designed to test the safety and feasibility of Autologous Muscle Derived Cells (AMDC) as a treatment for fecal incontinence in men and women. AMDC therapy seeks to allow remodeling of the external anal sphincter in patients with fecal incontinence from either defined structural defects to, or a generalized weakening of, the external anal sphincter. This treatment is hypothesized to reduce symptoms of fecal incontinence and improve patient quality of life by strengthening the external anal sphincter muscle. The study will treat a total of 50 patients with 250 x 10^6 cells each.

The primary objective is to determine the incidence of product- or procedure-related adverse events associated with the use of AMDC. Patients will be followed for 12 months.

All eligible patients consenting to study participation will have skeletal muscle tissue harvested using a needle biopsy during an initial outpatient procedure. The harvested muscle tissue will be placed in a hypothermic medium and transported to the manufacturer for processing in their cell processing facility in Pittsburgh, Pennsylvania, USA. The AMDC will be isolated and expanded in culture over several weeks to the final dose of 250 x 10^6 cells.

After reaching the desired concentration, the isolated and expanded cell population of AMDC will be quality tested and then cryopreserved and shipped back to the investigating physician. The physician will thaw and dilute the cells with saline. The resulting suspension will be injected into the patient's external anal sphincter in a brief outpatient procedure using a small needle under direct vision. Endoanal ultrasound may be used, at the physician's discretion to visualize the location of the injection needle within the external anal sphincter.

A detailed description of the study flow is illustrated in Appendix A.

2.0 Objectives of the Clinical Investigation

2.1 Primary Objective

The primary objective is to determine the incidence of product- or procedure-related adverse events associated with the use of AMDC within 12 months post-treatment.

2.2 Secondary Objectives

The secondary objectives are to study the effect of AMDC treatment for fecal incontinence on:

- Changes from baseline in the frequency and nature of incontinent episodes at 3, 6, and 12 months post-treatment as measured by a patient fecal incontinence diary
- Changes from baseline in Wexner incontinence score [1] (copy provided in Appendix B) at 3, 6, and 12 months post-treatment

- Changes from baseline in Fecal Incontinence Quality of Life Scale (FIQL) [2] (copy provided in Appendix C) scores at 3, 6, and 12 months post-treatment
- Changes from baseline in sphincter function as measured by anorectal manometry at 12 months
- Changes from baseline in sphincter morphology as measured by endoanal ultrasound at 12 months
- Safety as measured by adverse events

2.3 Claims and Intended Performance that are to be verified

AMDC treatment is intended to be safe and feasible for the treatment of fecal incontinence.

3.0 Product Description and Intended Use

3.1 Intended Use

AMDC is intended for use in external anal sphincter repair (ASR) for the treatment of fecal incontinence due to a weakened or injured external anal sphincter muscle. The purpose is to increase external sphincter functionality by injecting AMDC into the external sphincter muscle tissue.

3.2 General Product Description

[redacted]

Cook MyoSite will perform cell processing and preparation of cell suspensions for study use in their cell processing facility in Pittsburgh, Pennsylvania, USA. [redacted]

[redacted]

[redacted]

3.3 Summary Description of Procedures and Instructions for Use

3.3.1 Summary Description of Procedures

Muscle Biopsy

The biopsy procedure will involve minor surgery to collect a [redacted] muscle using a sampling needle. Prior to the biopsy, patients that are currently taking any form of anticoagulant medication must stop using the medication as per standard of care for outpatient surgery procedures. Muscle biopsies are obtained [redacted] using a percutaneous needle biopsy technique. Ultrasound imaging of the thigh may be used to aid in locating the proper muscle region and depth. The skin is prepared by shaving a small area at the site of the muscle biopsy, if necessary, and cleaning with an antimicrobial skin wash. The biopsy site is anesthetized with a local injection of 1% lidocaine (or other appropriate local anesthetic). A small incision of approximately 5 mm is made in the skin to allow the sterile needle to enter and remove [redacted] muscle tissue.

[redacted]

[redacted]

Isolation and Expansion of the Study Agent

After receipt at the cell processing center, desirable AMDC will be isolated from the tissue biopsy. [redacted]

[redacted]

Once the desired cell number has been achieved, quality tests following applicable local regulations assure the cells meet acceptance criteria for sterility, contaminants, cell viability, and functional integrity. [redacted]

Transportation and Storage of the Study Agent

The study agent must remain frozen and undiluted until ready for use. [redacted]

Dilution and Preparation for Injection

The 2 mL frozen study agent suspension is thawed and diluted [redacted] saline. The entire vial contents should be used for injection.

Cell Injection

The patient may receive local anesthesia at the injection site, as determined after discussion between the patient and physician. Using a small needle, multiple [redacted] percutaneous injections parallel to the anal canal will be performed to place the patient's own processed cells into the external anal sphincter. Endoanal ultrasound guidance may be used at the physician's discretion to assist with needle localization. [redacted]

3.3.2 Instructions for Use

The current study Procedure Guidelines, which will be provided to physicians and appropriately designated team members at the time of training, must be followed for step-by-step instructions for performing the following:
Obtaining the muscle biopsy
Packaging and shipping the muscle biopsy
Storing and handling requirements of the final AMDC product
Resuspending the final AMDC product
Performing the injection procedure

Muscle Biopsy

- Identify the target biopsy site.
- After cleaning and preparing the target biopsy site, anesthetize the skin and subcutaneous tissue with 1% lidocaine (or other appropriate local anesthetic), avoiding contact with muscle.
- Aseptically open the biopsy procurement supplies and prepare according to instructions.
- Incise the skin and deep fascia with scalpel blade.
- Insert the needle and use according to the manufacturer's instructions. Remove the needle and evacuate the specimen into the transportation biopsy medium vial. Close the wound and cover with an appropriate dressing.

Note: It may be necessary to repeat the sampling procedure from the same location to obtain sufficient muscle tissue.

Dilution and Preparation for Injection

[redacted]

Cell Injection

1. If applicable, prepare the injection site with administration of an appropriate local anesthesia.
2. Attach syringe containing thawed product suspension (as described in the instructions for dilution and injection) to the injection needle.
3. Insert the needle tip into the external anal sphincter and slowly inject the prepared suspension.
4. [redacted]
5. Ascertain the presence of bleeding or excessive trauma at the injection site.

3.4 Summary of Necessary Training and Experience

Training and experience needed for use of the product includes experience performing anorectal procedures and treatment of fecal incontinence. Study investigators will receive additional training related to the muscle biopsy and AMDC injection procedures as appropriate.

3.5 Description of the Necessary Medical or Surgical Procedures

Medical or surgical procedures used in this study include: skeletal muscle biopsy, cell injection into external anal sphincter, routine venipuncture (for blood-borne pathogen tests), pregnancy test (if applicable for women of childbearing age), and standard procedures for care of fecal incontinent patients, including anoscopy, sigmoidoscopy, digital rectal examination, anorectal manometry, and endoanal ultrasound. Refer to the Instructions for Use section regarding biopsy and injection procedures (Section 3.3.2). A full description of other procedures and schedule of events is contained in Section 6.7.

4.0 Preliminary Investigations and Justification

4.1 Literature Review and Justification

Please reference the Investigator's Brochure for a complete literature review and study justification.

4.2 Non-clinical Testing

Non-clinical tests were conducted in accordance with Good Laboratory Practice requirements or performed in compliance with verified methods and Standard Operating Procedures to maintain the integrity of the results. Please reference the Clinical Investigator's Brochure for a summary of non-clinical testing.

4.3 Previous Clinical Experience

Please reference the Investigator's Brochure for a complete description of previous clinical experience with AMDC.

5.0 Risk Analysis and Risk Assessment

Please reference the Investigator's Brochure for a summary of the complete risk analysis.

5.1 Risks and Foreseeable Adverse Product Effects

Risks of participation in the study include those associated with:

AMDC Injection: (Investigational procedure) Rare potential risks (<1%) include an allergic or immune response to AMDC (cells or components of the final formulation including bovine proteins, ampicillin, and gentamicin sulfate), and infection. Risk of allergic or immune response to the cells is expected to be minimal due to the use of autologous cells. Risk of allergic response to bovine proteins, ampicillin, and gentamicin sulfate used in AMDC production will be minimal since only trace amounts are expected to be in the final product. Other potential risks

(1-5%) include bleeding, infection, inflammatory response or irritation, pain or discomfort, worsening incontinence, diarrhea, constipation, and rectal obstruction or fecal retention.

Muscle Biopsy: (Non-standard care procedure) Potential risks (1-5%) include the possibility of bleeding, bruising, hematoma, infection, local pain or discomfort, delayed wound healing, and scarring.

Anoscopy, Sigmoidoscopy: (Standard care procedures) Potential risks include bleeding, infection, irritation, pain or discomfort, and perforation or damage of the intestinal wall.

Endoanal Ultrasound: (Standard care procedure) Potential risks include bleeding, infection, irritation, pain or discomfort, and perforation or damage of the intestinal wall.

Anorectal Manometry: (Standard care procedure) Potential risks include bleeding, infection, irritation, pain or discomfort, and perforation or damage of the intestinal wall.

Venipuncture: (Standard care procedure) Potential risks include bleeding, bruising, infection, light-headedness, and pain or discomfort at the site where blood is drawn.

Additional risks are expected to be comparable to those associated with standard treatment using bulking injections [3, 4]. These include the possibility of fecal retention and infection. In addition, mild reactions such as swelling and local irritation may be associated with local anesthetics used during the injection procedure.

Because this study includes experimental procedures, not all risks and outcomes can be foreseen.

5.2 Methods to Minimize Risks

The procedure for proper deployment of the product at the intended site is described in the Summary Description of Procedures and the Instructions for Use (Sections 3.3.1 and 3.3.2). Only qualified physicians experienced in performing anorectal procedures will inject the product. Appropriate patient selection and adherence to, and training on, the research protocol are necessary to reduce product- and procedure-related risk. Routine venipuncture will be performed by qualified personnel.

Injection of AMDC will occur under direct vision. The presence of bleeding or puncture will be ascertained following injection. In addition, this investigation includes a high level of monitoring. The risks of continued incontinence, infection, and allergic reaction to the injected reagents will be assessed through patient report, a patient fecal incontinence diary that will be kept at various time points throughout the study, and clinical follow-up at 3, 6, and12 months after treatment. Patients will be contacted by phone 24-48 hours and one month after injection to assess for adverse events.

6.0 Design of the Clinical Investigation

6.1 Type of Investigation

The proposed investigation will be a prospective, non-randomized, multicenter study to determine the safety and feasibility of AMDC in the treatment of patients with fecal incontinence. The study will treat a total of 50 patients with a dose of 250 x 10^6 cells.

6.2 Rationale

Despite considerable advances in both the pharmacological and device-related therapeutic strategies, a successful treatment for fecal incontinence that can apply to all patients remains to be developed. Fecal incontinence thus continues to be a debilitating and embarrassing condition for patients world-wide.

AMDC consists of cells derived from skeletal muscle tissue that are expanded *ex vivo*. [redacted] Clinical and non-clinical studies evaluating AMDC have supported these conclusions for the proposed cell therapy.

6.3 Inclusion Criteria

A patient may be enrolled in the study if the following inclusion criteria are met:

- Patient has primary symptoms of fecal incontinence, as confirmed by patient medical history and physical examination, including visual inspection, digital rectal examination, anoscopy and/or sigmoidoscopy
- Patient has a Wexner score of ≥ 9 at baseline
- Etiology of FI is related, at least in part, to external anal sphincter dysfunction, as evidenced by external anal sphincter defect (or abnormality) observed on EAUS and/or lower than normal manometric maximum squeeze pressure of <80mmHg
- Patient has failed conservative treatment (e.g. dietary modification, antidiarrheal medications, pelvic floor muscle training, biofeedback) for at least 1 month prior to enrollment

6.4 Exclusion Criteria

A patient must not be included in the study if any of the following criteria are true at the time of enrollment:

Gastrointestinal:

- Patient has undergone a gracilis neosphincter or insertion of an artificial bowel sphincter

- Patient has Inflammatory Bowel Disease (Crohn's disease, ulcerative colitis)
- Patient has a non-viable mucosal lining along the anal tract
- Patient has known significant pelvic floor prolapse, significant genitourinary prolapse beyond the introitus, significant symptomatic rectocele, or evidence of significant rectal evacuation disorder leading to post-defecatory leakage
- Patient has history of radiation treatment to the external anal sphincter or adjacent structures
- Patient does not agree to refrain from anoreceptive intercourse for the duration of the study

General:

- Patient is less than 18 years of age
- Patient is pregnant, breastfeeding, or plans to become pregnant during the course of the study
- Patient is morbidly obese (BMI ≥ 35)
- Patient has a neuromuscular disorder (e.g., muscular dystrophy, multiple sclerosis, fibromyalgia)
- Patient has uncontrolled type I or type II diabetes
- Patient has history of neoplasia within 5 years prior to enrollment, except for a cancer that was determined to be local occurrence only, such as basal cell carcinoma, or is receiving or planning to receive anti-cancer or anti-angiogenic drugs.
- Patient is not suitable for muscle biopsy as determined by physician
- Patient tests positive for Hepatitis B (required tests: Hepatitis B Surface Antigen [HBsAg] and Anti-Hepatitis B Core Antibody [Anti-HBc]), Hepatitis C (required test: Hepatitis C Antibody [Anti-HCV]), HIV (required tests: HIV Type 1 and 2 Antibodies [Anti-HIV-1, 2]), and syphilis
- Patient has known bleeding diathesis or uncorrected coagulopathy
- Patient has known allergy or hypersensitivity to bovine proteins or allergens, gentamicin sulfate, or ampicillin that medically warrants exclusion as determined by physician
- Patient has a compromised immune system due to disease state, chronic corticosteroid use or other immunosuppressive therapy
- Patient has any condition that would preclude treatment due to contraindications and/or warnings of concomitant medications or listed in the experimental product labeling
  Patient is simultaneously participating in another investigational drug or device study or the patient has completed the follow-up phase for the primary endpoint of any previous study less than 30 days prior to the first evaluation in this study
- Patient is unable or unwilling to provide informed consent
- Patient is unable or unwilling to commit to the follow-up procedures
- Patient has a medical condition or disorder that may limit life expectancy < two years or that may cause non-compliance with the protocol (e.g. unable to perform self-evaluations and/or accurately report medical history, incontinence symptoms, and/or data)

At Time of Cell Delivery:

- Patient is febrile (defined as temperature ≥ 38.5° C)
- Patient has current infection
- Patient has active anal fissure, anal fistula, rectal prolapse (full-thickness), or grade III or IV hemorrhoids

6.5 Point of Enrollment

Patients who meet the inclusion/exclusion criteria are eligible for entry into the study and will have the study protocol and potential risks and benefits of their participation in the study explained to them by the research coordinator and/or physician(s) as appropriate per institutional policy. Informed consent will be obtained in accordance with ICH GCP and applicable regulations, and each patient who agrees to participate in this study will be required to sign an informed consent document prior to any study procedure. Official enrollment will occur at the time of the biopsy.

6.6 Sample Size and Dose Allocation

The study will be undertaken at up to five investigative sites. A total of 50 patients will be treated with AMDC. There will be a minimum 1 week delay between the AMDC injection procedures for the first 5 patients.

All patients will receive a cell dose of 250 x 10^6 (± 20%) cells (refer to section 7.3 Non-conforming product injection). The Manufacturer will generate the appropriate cell dose and ship it to the Investigator for injection. All AMDC products will be transported in identical vials with the same volume of transport media and reconstituted to the same final volume prior to injection. Vials will be identified by a unique product lot number, which includes the patient identification number, patient initials, and date of collection.

6.7 Description of Methods at Patient Visits

The schedule of exams specific to study visits (time points) is provided in Table 6-1. A detailed study flow diagram is provided in Appendix A. Note that the time windows indicated for specific visits are suggested guidelines, not absolute requirements. The exams/tests specified at each visit (study time point) may be combined in any number of actual visits to accommodate site and patient scheduling as necessary.

Regarding study medications, there are no specific medication requirements for patients participating in this study. Patients are to be prescribed medications according to the standard of care at the respective investigative site. To the greatest degree possible, a patient's medication regimen related to fecal incontinence should be maintained constant during the entire course of the study. Patient medication usage will be captured in the medication log.

Table 6-1: Exam Visit Schedule

	Pre-enrollment Screening and Baseline[1]	Biopsy[1]	AMDC Injection Procedure	Post-treatment Follow-up[1]				
Study Time Point	**Week -16 to -8**	**Week -8 to -6**	**Day 0**	**Day 1 to 2**	**Month 1**	**Month 3**	**Month 6**	**Month 12**
	Visit 1	**Visit 2**	**Visit 3**	**Phone**	**Phone**	**Visit 4**	**Visit 5**	**Visit 6**
Informed Consent	X							
Patient History	X							
Medications Log	X	X	X	X	X	X	X	X
Blood Borne Pathogens (HBV, HCV, HIV and syphilis)[2]	X	X						
Pregnancy Test[3]	X	X	X					
Clinical Assessment[4]	X		X			X	X	X
FIQL[5]	X					X	X	X
Wexner Score	X					X	X	X
Patient Fecal Incontinence Diary[6]		X	X			X	X	X
Endoanal Ultrasound	X[7]							X
Anorectal Manometry	X[7]							X
Muscle Biopsy		X						
AMDC Injection			X					
Phone Contact				X	X			
Adverse Events	X	X	X	X	X	X	X	X

[1] Exams/assessments may be completed at multiple actual visits as necessary to accommodate patient and hospital scheduling.

[2] If the biopsy procedure takes place more than 30 days after the blood-borne pathogens tests were completed during screening, the blood borne pathogen tests (Hepatitis B, Hepatitis C, HIV, and syphilis) must be repeated before the biopsy procedure to confirm the patient's continued eligibility for study participation.

[3] Pregnancy test is not required if the patient has had a previous hysterectomy and/or is post-menopausal.

[4] Clinical assessment (physical examination) includes visual inspection, digital rectal examination, and anoscopy and/or sigmoidoscopy at physician's discretion.

[5] Fecal Incontinence Quality of Life Scale (FIQL)

[6] The baseline Patient Fecal Incontinence Diary will be given out after the muscle biopsy and is to be completed prior to, and returned at, the injection procedure. A diary will be given at the injection and returned at the 3-month follow-up visit. During post-treatment follow-up, diaries are to be completed approximately 28-days prior to, and returned at, each designated visit.

[7] Previous endoanal ultrasound and anorectal manometry exam results may be used for the baseline assessments as long as they: 1) were completed within 6 months prior to enrollment, 2) collected all required data, and 3) the patient did not undergo any procedures or change in condition since the exam that, in the physician's discretion, would be likely to invalidate the previous results.

6.7.1 Visit 1 (Week -16 to -8): Pre-enrollment Screening and Baseline

Informed consent will be obtained and patient medical history will be collected. A physical examination (clinical assessment), including a visual inspection, digital rectal examination, and anoscopy and/or sigmoidoscopy (at physician's discretion), will be performed. Blood samples will be collected to assess for blood-borne pathogens (Hepatitis B, Hepatitis C, HIV, and syphilis). If the biopsy procedure takes place more than 30 days after the blood-borne pathogen tests were completed during screening, the blood-borne pathogen tests (i.e. Hepatitis B, Hepatitis C, HIV, and syphilis) must be repeated before the biopsy procedure to confirm the patient's continued eligibility for study participation. If applicable, a urine sample will be collected from female patients for pregnancy testing (pregnancy test is not required if the patient has had a previous hysterectomy and/or is post-menopausal). During the visit, the patient will complete the FIQL and Wexner score questionnaires (administered by a member of the research staff). A log of the patient's current medications will be started. Patients will also be instructed not to change (to the greatest degree possible) their medication regimen, and other coping mechanisms, related to their fecal incontinence condition.

In addition, endoanal ultrasound and anorectal manometry tests will be performed prior to the biopsy. Previous exam results may be used for the baseline assessments as long as: 1) they were completed within 6 months prior to enrollment, 2) they collected all required data, and 3) the patient did not undergo any procedures or have any change in condition since the exam that, in the physician's opinion, would be likely to invalidate the previous results.

All pre-enrollment screening and baseline assessments (e.g. clinical assessment, urine test, ultrasound, manometry, and questionnaires) are recommended to be completed within eight weeks prior to enrollment. Blood tests must be performed within 30 days prior to the biopsy. These blood tests will be repeated prior to any additional biopsies, if more than one biopsy is required. Per manufacturing requirements, patients must be negative for the blood-borne pathogens of hepatitis B (required tests: Hepatitis B Surface Antigen [HBsAg] and Anti-Hepatitis B Core Antibody [Anti-HBc]), Hepatitis C(required test: Hepatitis C Antibody [Anti-HCV]),HIV (required tests: HIV Type 1 and 2 Antibodies [Anti-HIV-1, 2]), and syphilis. At this point the patients will have completed all the necessary screening assessments and, if they meet all entry criteria, may now be enrolled into the study and can be scheduled for the muscle biopsy.

6.7.2 Visit 2 (Week -8 to -6): Biopsy

After patient eligibility is confirmed, patients will return to the clinic for an outpatient procedure in which muscle tissue is obtained using a needle biopsy technique [redacted]. Note that several passes of the biopsy needle may be required to obtain a satisfactory sample of muscle tissue. Additionally, if the first biopsy does not produce an adequate sample for product isolation, it may be necessary for the patient to return for another biopsy procedure. [redacted] If appropriate, patients will also have a urine sample collected for pregnancy testing, which would be repeated at any additional biopsy visits if more than one biopsy is required. The medication log will be updated if necessary and adverse events will be recorded and reported as appropriate. Additionally, patients will be given a 28-day diary to report fecal incontinence data and instructions on how to complete the diary. The diary should be started approximately 1

week after the biopsy procedure, completed during the subsequent 28 days, and returned to the site at the next scheduled visit (injection visit).

6.7.3 Visit 3 (Day 0): AMDC Injection Procedure

[redacted] after the muscle biopsy, patients will return to the clinic for a brief outpatient procedure. Prior to injection, if appropriate, patients will also have a urine sample collected for pregnancy testing. Patients will also have their temperature measured and be assessed for signs of infection and changes in anorectal condition that may affect the "At Time of Cell Delivery" exclusion criteria. After confirming eligibility, the AMDC product will be prepared and injected into the external anal sphincter in accordance with instructions for use (as described in Section 3.3). Post-injection, injection sites will be inspected for the presence of bleeding or excessive trauma.

The medication log will be updated if necessary and adverse events will be recorded and reported as appropriate. Patients will be reminded not to change (to the greatest degree possible) their medication regimen, and other coping mechanisms, related to their fecal incontinence condition. Patients will be given a 28-day diary to report fecal incontinence data. The diary should be completed during the 28 days leading up to, and returned to the site at, the next scheduled visit (3 Month Follow-up Visit).

6.7.4 Phone Contact (Day 1 to 2): Post-treatment Follow-up

Between 24 and 48 hours after treatment, patients will be contacted by phone to determine if any adverse events have occurred and if the patient has any updates for the medication log.

6.7.5 Phone Contact (Month 1, ±1 week): Post-treatment Follow-up

One month after the AMDC injection procedure the patients will be contacted by phone to determine if any adverse events have occurred and if the patients have any updates for the medication log.

6.7.6 Visit 4 (Month 3, ±1 week): Post-treatment Follow-up

Patients will return to the clinic for evaluation. A physical examination (clinical assessment), including a visual inspection, digital rectal examination, and anoscopy and/or sigmoidoscopy (at physician's discretion), will be performed. During the visit, the patient will complete the FIQL and Wexner score questionnaires (administered by a member of the research staff). The medication log will be updated if necessary and adverse events will be recorded and reported as appropriate.

Patients will return their recently completed 28-day diary and will be given another 28-day diary to report fecal incontinence data. The diary should be completed during the 28-days leading up to, and returned to the site at, the next scheduled visit (6 Month Follow-up Visit). Patients may be contacted as a reminder when to start the diary.

6.7.7 Visit 5 (Month 6, -2, +4 weeks): Post-treatment Follow-up

Patients will return to the clinic for evaluation. A physical examination (clinical assessment), including a visual inspection, digital rectal examination, and anoscopy and/or sigmoidoscopy (at physician's discretion), will be performed. During the visit, the patient will complete the FIQL and Wexner score questionnaires (administered by a member of the research staff). The medication log will be updated if necessary and adverse events will be recorded and reported as appropriate.

Patients will return their recently completed 28-day diary and will be given another 28-day diary to report fecal incontinence data. The diary should be completed during the 28-days leading up to, and returned to the site at, the next scheduled visit (12 Month Follow-up Visit). Patients may be contacted as a reminder when to start the diary.

6.7.8 Visit 6 (Month 12, -2, +4 weeks): Post-treatment Follow-up

Patients will return to the clinic for evaluation. A physical examination (clinical assessment), including a visual inspection, digital rectal examination, and anoscopy and/or sigmoidoscopy (at physician's discretion), will be performed. During the visit, the patient will complete the FIQL and Wexner score questionnaires (administered by a member of the research staff). The medication log will be updated if necessary and adverse events will be recorded and reported as appropriate. Patients will return their recently completed 28-day diary. Additionally, an endoanal ultrasound and an anorectal manometry evaluation will be performed.

After completing the 12 month follow-up, patients will be considered as having completed the study.

6.8 Criteria and Procedures for Withdrawal

A patient may decide to withdraw from the investigation at any time without prejudice or loss of care. An effort will be made to obtain, in writing, notification from patient of desire to withdraw. The Investigator may also decide to withdraw the patient from the investigation at any time based on medical judgment. In these instances, the appropriate case report forms and study exit form must be completed. The reason why the patient has withdrawn shall be stated on the study exit form.

If a patient should discontinue the study for any reason, a study exit form will be completed. On this form, the reason for discontinuation will be indicated (e.g. death, lost to follow-up, withdrawal, or completion of study). Space is also provided for documentation of further explanation of discontinuation.

In the event a patient is lost to follow-up or fails to appear for scheduled post-treatment assessment, efforts will be made to locate the patient before filing a study exit form, and these efforts will be documented.

If a patient receives treatment other than the study procedure (e.g. receives an injection of a bulking agent, or completes a surgery) before the completion of all scheduled follow-ups, then the patient will be withdrawn from the study and follow-up will be terminated. In this event, an attempt to collect safety and effectiveness measures prior to additional procedures will be made. The patient will be considered withdrawn on the study exit form.

6.9 Limitations of the Study

The number of patients for this study is too small to definitively demonstrate safety or effectiveness of the treatment. Since all the possible variables that might affect the outcome of this treatment are not known at this point, the results may vary. However, this study may give indications of the safety and value of this treatment method, as well as provide information and data necessary to undertake a larger clinical trial.

6.10 Safety Monitoring and Reporting of Adverse Events

A Data Safety Monitoring Board (DSMB) consisting of independent physicians, who are not investigators in the study, nor have a perceived conflict of interest with the conduct and administration of the investigation, may be convened to evaluate investigation progress and review adverse events.

An independent Clinical Events Committee (CEC) consisting of physicians, who are not investigators in the study, nor have a perceived conflict of interest with the conduct and administration of the study, may be established to adjudicate clinical events reported during the study. This adjudication will be performed according to standard operating procedures to assess whether the events were due to a pre-existing or unrelated condition, procedure-related, technique-related, and/or product-related.

Regularly scheduled monitoring, including on-site visits, will be conducted, in part, for identification of adverse events and assurance that they are accurately reported within the appropriate time frame.

Definitions for adverse events were derived from the ICH guideline on Clinical Data Safety Management: Definitions and Standards for Expedited Reporting, Section II: Definitions and Terminology Associated with Clinical Safety Experience. Definitions are provided in Appendix D.

All adverse events (or adverse experiences), related or unrelated to the AMDC product or procedure, should be reported on the Event case report form within ten days of the site's knowledge of the adverse event.

All serious adverse events, serious adverse drug reactions, and serious unexpected adverse drug reactions related to the AMDC product or procedure shall be reported immediately to the data coordinating center (Cook Research Incorporated), who will inform the Sponsor accordingly. All adverse events and adverse drug reactions will be investigated in collaboration with the Investigator involved as well as with the Principal Investigator, as needed (i.e. adjudication will be carried out according to predetermined procedures when necessary).

In accordance with regulatory requirements within each country, appropriate reports will be made to inform the investigators of adverse effects attributable to AMDC. The Investigator will be responsible for informing the local ethics committee accordingly, whereas the Sponsor will inform the competent authority according to reporting regulations.

7.0 Statistical Considerations

7.1 Sample Size Calculations

Fifty patients will be enrolled in this study. This population is sufficient to demonstrate the feasibility and potential efficacy of treatment and methods of AMDC delivery in patients with fecal incontinence. In addition, information concerning the safety of the treatment, likely complications, and potential utility of the cell therapy can be gathered with this population.

7.2 Analysis Plan

Endpoints will be summarized using frequency tables, means and standard deviations, 95% confidence intervals, and/or medians and ranges. Although it is expected that the study will have too few patients, exploratory analyses of subgroups and covariates may be performed to investigate their relationship to AMDC treatment and to generate hypothesis and pilot data for future larger studies.

7.3 Non-conforming product injection

Because of the personalized nature of the product, it is possible some products may meet all safety specifications but not meet all release specifications related to cell type and/or target dose (sub-optimal). Therefore, in order to allow patients with sub-optimal products to be treated, these sub-optimal products may be released for treatment of these patients at the physician's discretion and if the patient agrees.

Additionally, it is possible that an approved product is released for use, but due to unforeseen circumstances, is not able to be injected within the current product expiration period (60 days). In these instances, the product may be treated as a non-conforming product and released for use at the physician's discretion and with patient consent following confirmation from the Sponsor and from the regulatory authority that there are no concerns with safety or product integrity.

8.0 Deviations from Clinical Investigation Plan

Deviations or non-compliances will be recorded together with an explanation. Deviations that impact the rights, welfare or safety of patients shall be reported to the sponsor, regulatory authorities and Ethics Committee/REB as required.

The reasons for withdrawal and discontinuation of any patient from the study should be recorded, if possible. If such discontinuation is because of problems with safety or lack of effectiveness, that patient should still be followed-up in the study, if possible.

9.0 Safety Monitoring

All individual Investigators participating in the study are entitled to stop enrolling patients in case of disagreement with a delivered official decision by DSMB. If this should occur, the individual Investigator (Center) will not enroll any more patients, but will continue to follow those already enrolled according to the protocol. However, cases already included in the study remain in the population of cases analyzed.

10.0 Privacy, Confidentiality, and Ethical Considerations

Patient confidentially will be maintained during the clinical study in a way to ensure that information can always be tracked back to the source data through patient enrollment number and patient initials (if available). Data relating to the study may be made available to third parties (as an audit performed by regulatory authorities) provided that data is treated confidentially and the patient's privacy is intact.

Study patients will be assigned a unique enrollment number, and will be identified to the Sponsor only by this unique enrollment number and patient initials. Only de-identified patient information will be collected by the Local or Central Monitor.

De-identified health information will be used by researchers involved in the study. "Researchers" include the patient's physician and the staff of collaborators, Investigators in other locations studying these products, representatives of Cook MyoSite (the Sponsor and Manufacturer), and representatives from Cook Research Incorporated to assist in research.

These data will be used to gain additional experience about these products, and to advance medical knowledge by making presentations and writing articles about the study. These data may also be reviewed by government agencies that watch over research and approve medical products for use. If the product will be used in other countries, these data may be reviewed by similar agencies in those countries.

These data may also be combined with health information about other patients. The Sponsor or their designee will keep all the data in an ongoing database of information about the products so that information can be studied and analyzed. When the follow-up period of the study is over, no new information about individual patients will be added, but review of the data may continue. If a presentation is made, or reports and articles are written about this study, only de-identified information will be used.

For ethical considerations, all patients will be required to sign a consent indicating their willingness to participate and that they have been fully informed of the risks and benefits of participation. In addition, the study will be conducted under supervision of an ethical review committee and in compliance with the ICH Guidelines for Good Clinical Practice, the ISO 14155 and the Declaration of Helsinki.

11.0 Data Reporting and Record Retention

All study records and reports will be kept in accordance with applicable local and global regulations. The Sponsor will be notified before destruction (shredding) of these files.

Progress reports and a final report at the conclusion of the clinical study will be submitted by the Principal Investigators and Sponsor to the regulatory bodies as required by local regulations. All participating Principal Investigators will approve the Final Report. If an Investigator does not agree with the conclusion and will not sign the Final Report, (s)he must state the reasons for this. Until a Final Report has been formulated and approved by all of the participating Investigators, the Protocol and the study data are confidential and must not be published except for approved interim results. A copy of the Final Report will be sent to the Ethics Committees.

12.0 Publication Policy

The Principal Investigator and/or Institution shall furnish the Sponsor with a written copy of any proposed publication or presentation of material relating to the study at least thirty (30) days in advance of the date of the proposed first submission for publication or presentation. Within such thirty (30) day period, the Sponsor shall review the material and advise Principal Investigator and/or Institution as to whether it contains any confidential information which must not be disclosed and as to whether the proposed publication date is in conflict with Cook's publication strategy. If the material is deemed to contain confidential information, the Principal Investigator and/or Institution shall edit the material in accordance with the recommendation of Cook before publication or presentation. If the proposed publication date is in conflict with Cook's publication strategy for the Study Product, Cook and Institution will negotiate a mutually agreeable publication date for the proposed publication.

In addition to the foregoing, in the event that the publication discloses patentable material, Principal Investigator and/or Institution shall grant Sponsor sufficient time, not to exceed ninety (90) days, to obtain proprietary rights protection for any material prior to publication or presentation. Cook's review of any proposed publication or presentation materials shall not relieve Principal Investigator and/or Institution from any of its obligations regarding confidential information. Any and all publications or presentations of material relating to the Study shall require the express written permission of the Sponsor, which will not be unreasonably withheld.

13.0 Data Collection

Data will be collected on a secure web-based electronic case report form (eCRF) and entered by qualified personnel. Patient data will be collected and entered by the investigative site into an eCRF system. This is a secure, web-based system, allowing those with permission to access data from any location at any time. Site personnel are required to have unique login names and passwords in order to enter patient data, and, in accordance with 21 CFR Part 11, the eCRF system creates a secure, computer-generated, time stamped audit trail to record the date and time of operator entries and actions that create, modify, or delete electronic records.

14.0 Study Administration and Information

For additional contact information, please refer to Appendix E.

14.1 Study Administration

The study will be conducted in compliance with ISO 14155 and the International Conference of Harmonization Guideline for Good Clinical Practice. All cell and tissue processing will comply with quality standards specified in applicable local regulations.

14.2 Sponsor and Manufacturer

Cook MyoSite, Incorporated
105 Delta Drive
Pittsburgh, PA 15238
USA

14.3 Data Coordinating Center/Monitor

Cook Research Incorporated
1 Geddes Way
West Lafayette, IN 47906
USA

14.4 Investigators

A current list of clinical investigators along with their contact and site information is provided in Appendix E. The contact information will be updated and maintained by the Data Coordinating Center.

14.5 Monitoring Arrangements

The conduct of the clinical trial will be supervised through a process of remote and on-site monitoring. The data coordinating center will be responsible for monitoring the study for adverse events. The possible adverse events associated with this study are listed in Section 6.10, Risk Analysis and Risk Assessment are discussed in Section 5.

Monitoring will verify that clinical study activities comply with relevant regulations. These activities shall be consistent with requirements as specified in the Declaration of Helsinki, International Conference on Harmonization, Good Clinical Practices, and other regulations in force in the country where the study takes place.

Monitoring will ensure:

- The study is being conducted in accordance with the protocol, relevant regulations and company policies
- Adequate protection of the rights and safety of informed human patients involved in the clinical study

- Quality and integrity of data
- Proper use, treatment, and attitude toward the investigational material and to observe the use of the material to learn the opportunities for improvement

The study will be monitored in accordance with written standard operating procedures. [redacted]

14.6 Data Management and Quality Assurance

Patient demographics, procedural information and follow-up data will be collected in a secure electronic database on standardized case report forms. All data are verified for accuracy and consistency, and all data edits are tracked with a verifiable audit trail.

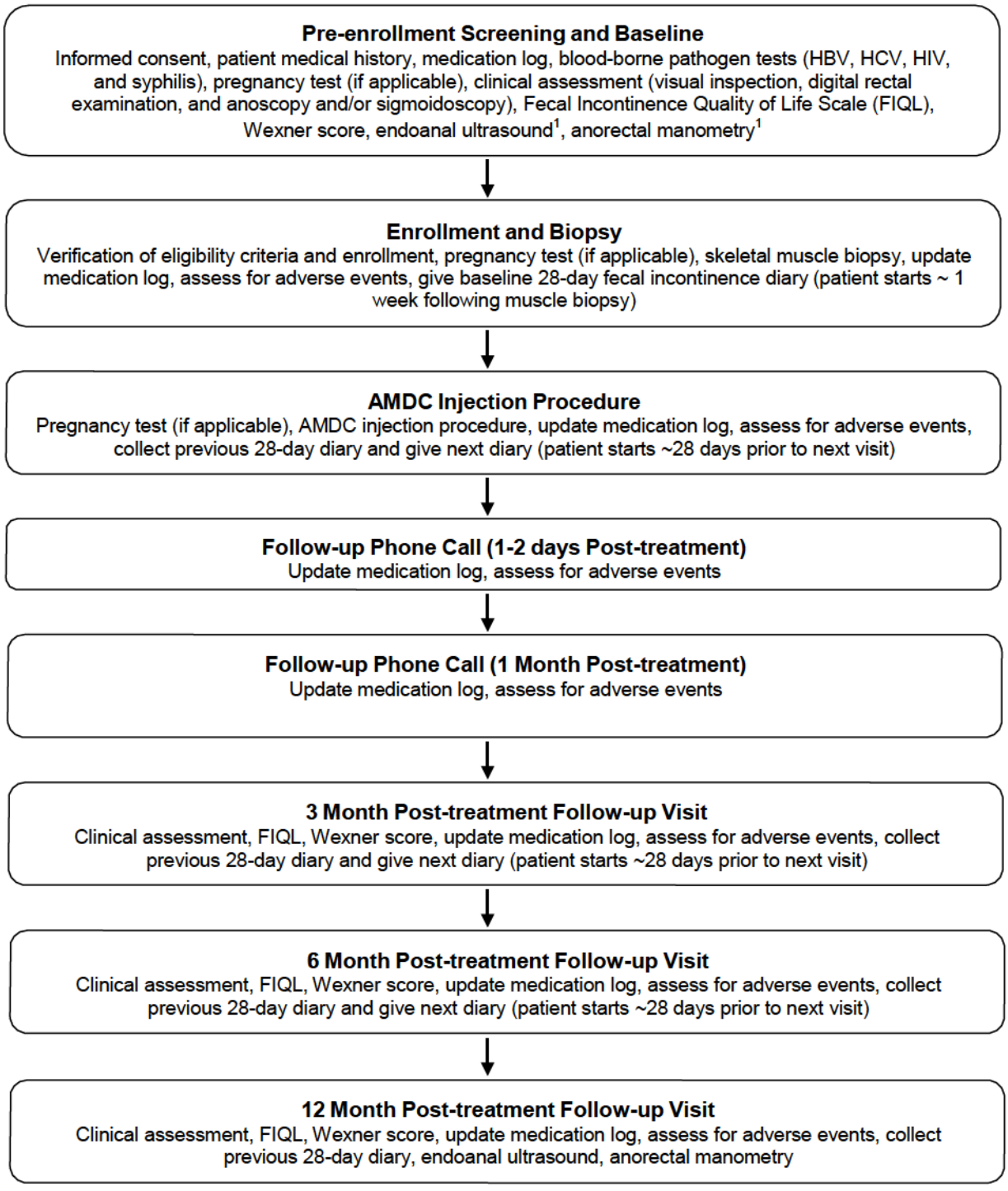
15.0 Approvals and Agreements

The sponsor and the principal clinical investigators for each site shall agree to this document and any modifications. A justification for any modifications will be documented. Approval and agreement will be indicated by signing and dating this document.

16.0 References

1. Jorge JM, Wexner SD. Etiology and management of fecal incontinence. Dis Colon Rectum 1993;36(1):77-97.
2. Rockwood TH, Church JM, Fleshman JW, Kane RL, Mavrantonis C, Thorson AG, Wexner SD, Bliss D, Lowry AC. Fecal Incontinence Quality of Life Scale: quality of life instrument for patients with fecal incontinence. Dis Colon Rectum. 2000;43(1):9-16.
3. Maeda Y, Laurberg S, Norton C. Perianal injectable bulking agents as treatment for faecal incontinence in adults. Cochrane Database Syst Rev. 2010;12(5):CD007959.
4. Luo C, Samaranayake CB, Plank LD, Bissett IP. Systematic review on the efficacy and safety of injectable bulking agents for passive faecal incontinence. Colorectal Dis. 2010;12(4):296-303.

APPENDIX A: Detailed Study Flow Diagram



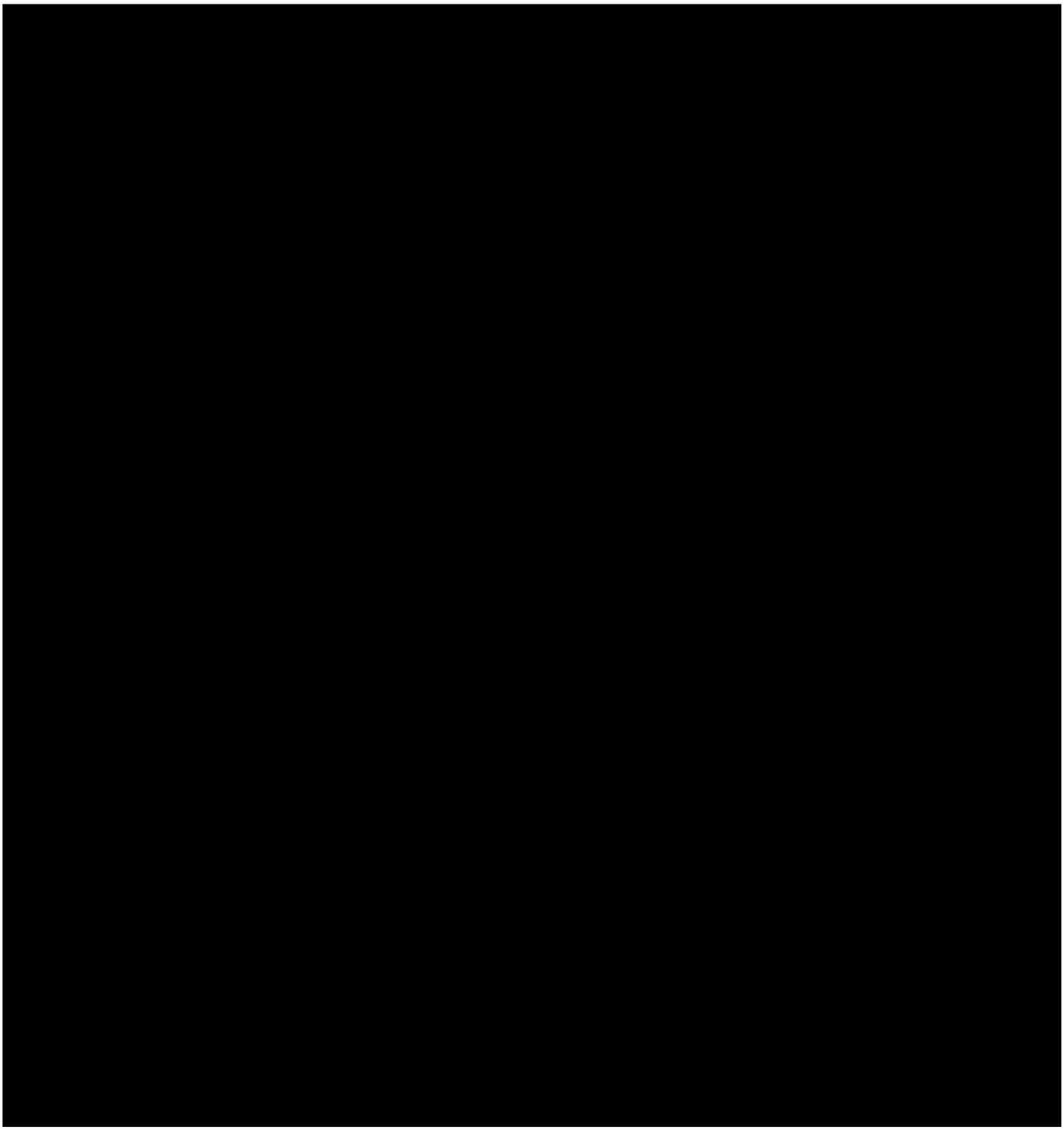
[1] Previous exam results may be used for the baseline assessments as long as they 1) were completed within 6 months prior to enrollment, 2) collected all required data, and 3) the patient did not undergo any procedures or change in condition since the exam that, in the physician's discretion, would be likely to invalidate the previous results.

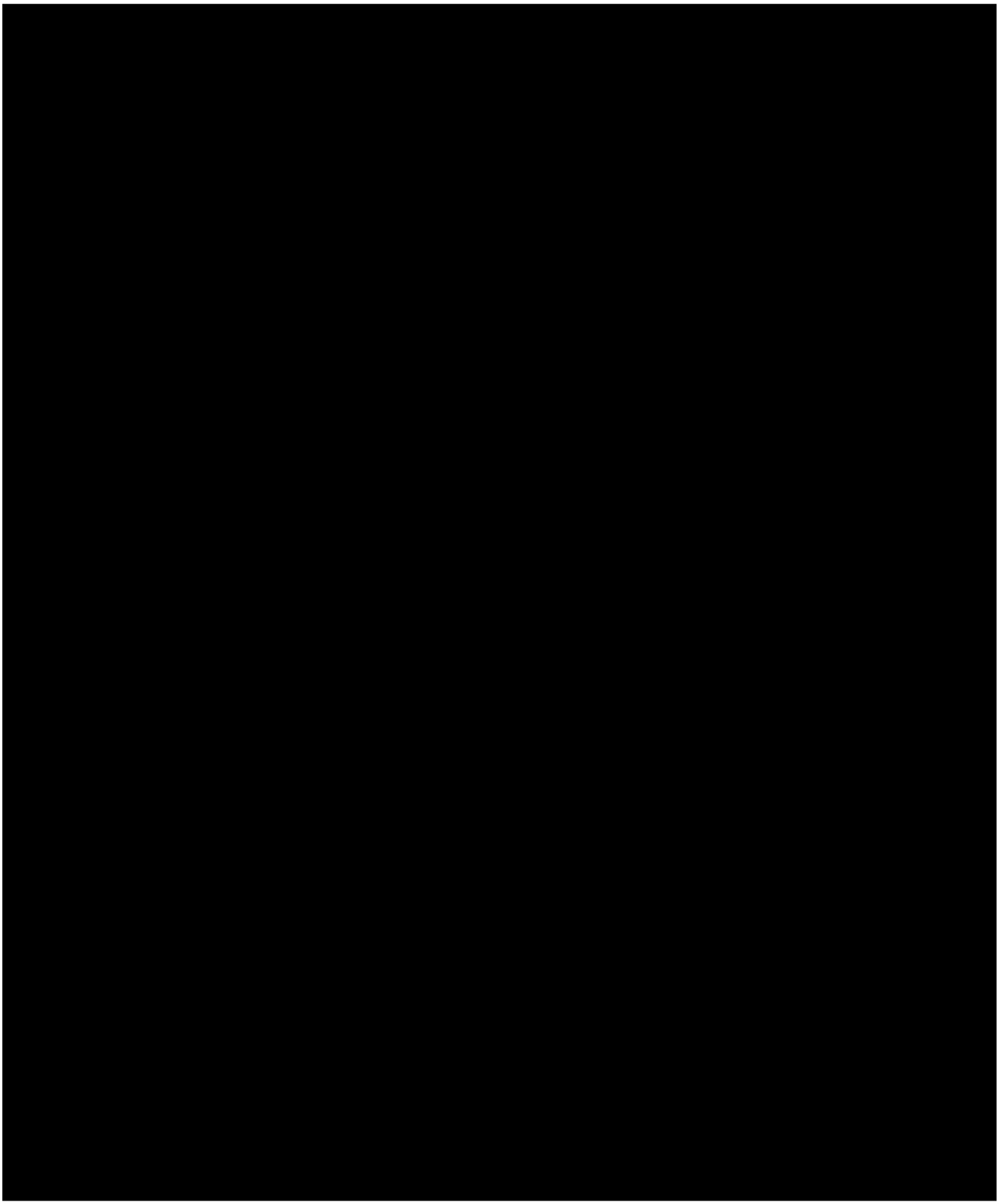
APPENDIX B: Wexner Score

Wexner Score [1]

APPENDIX C: Fecal Incontinence Quality of Life Scale

Fecal Incontinence Quality of Life Scale (FIQL) [2]





APPENDIX D: Definitions

Adverse Event or Adverse Experience

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical or biologic product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Adverse Drug Reaction

An adverse drug reaction (ADR) is any noxious and unintended response to a medicinal product related to any dose where there is a reasonable possibility of a causal relationship, i.e., the relationship cannot be ruled out.

Unexpected Adverse Drug Reaction

An adverse reaction, the nature and severity of which is not consistent with the applicable product information contained in the Investigators Brochure.

Serious Adverse Event or Serious Adverse Drug Reaction

Any events or drug reactions that, either due to their serious nature or due to the significant, unexpected information they provide, justify expedited reporting. A serious adverse event is defined as any event which meets any of the following criteria:

Death: An event, which results in the death of a patient.

Life Threatening Adverse Event: An event that if untreated, would lead directly to the death of the patient.

Hospitalization: An event that results in an admission to the hospital for any length of time.

Prolongs hospitalization: An event, which occurs while the study patient is hospitalized and prolongs the patient's hospital stay (due to potential disability, danger to life, or the event is terminal).

Causes persistent or significant disability or incapacity: An event that leads to a persistent or permanent disabling condition, congenital anomaly or birth defect.

Severity

Severity is a clinical determination of the intensity of a specific event. The event itself may be of relatively minor clinical significance. Severity is not the same as "serious", which is based on outcome or action criteria associated with events that pose a threat to a patient's life or functioning.

Relationship to AMDC

A determination will be made of the relationship (if any) between an adverse event and the AMDC treatment. The determination will be referred to a clinical events committee as needed. A causal relationship is present if a determination is made that there is a reasonable possibility that the adverse event may have been caused by the AMDC treatment. Adverse events meeting this criterion will be reported as an adverse drug reaction. If the event also meets one of the criteria for classification as “serious”, it will be reported as a serious adverse drug reaction.

APPENDIX E: Contact Information

Sponsor and Manufacturer

Cook MyoSite, Incorporated
105 Delta Drive
Pittsburgh, PA 15238
USA

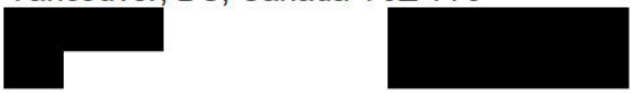
Contacts:

Data Coordinating Center/Monitor

Cook Research Incorporated
1 Geddes Way
West Lafayette, IN 47906
USA

Qualified Medical Expert for the Sponsor

Manoj J. Raval, MD, MSc, FRCSC
Department of Surgery, St. Paul's Hospital
Room C320, 1081 Burrard Street
Vancouver, BC, Canada V6Z 1Y6



Clinical Investigators and Sites (current list)

St. Paul's Hospital
1081 Burrard Street
Vancouver, BC, Canada V6Z 1Y6

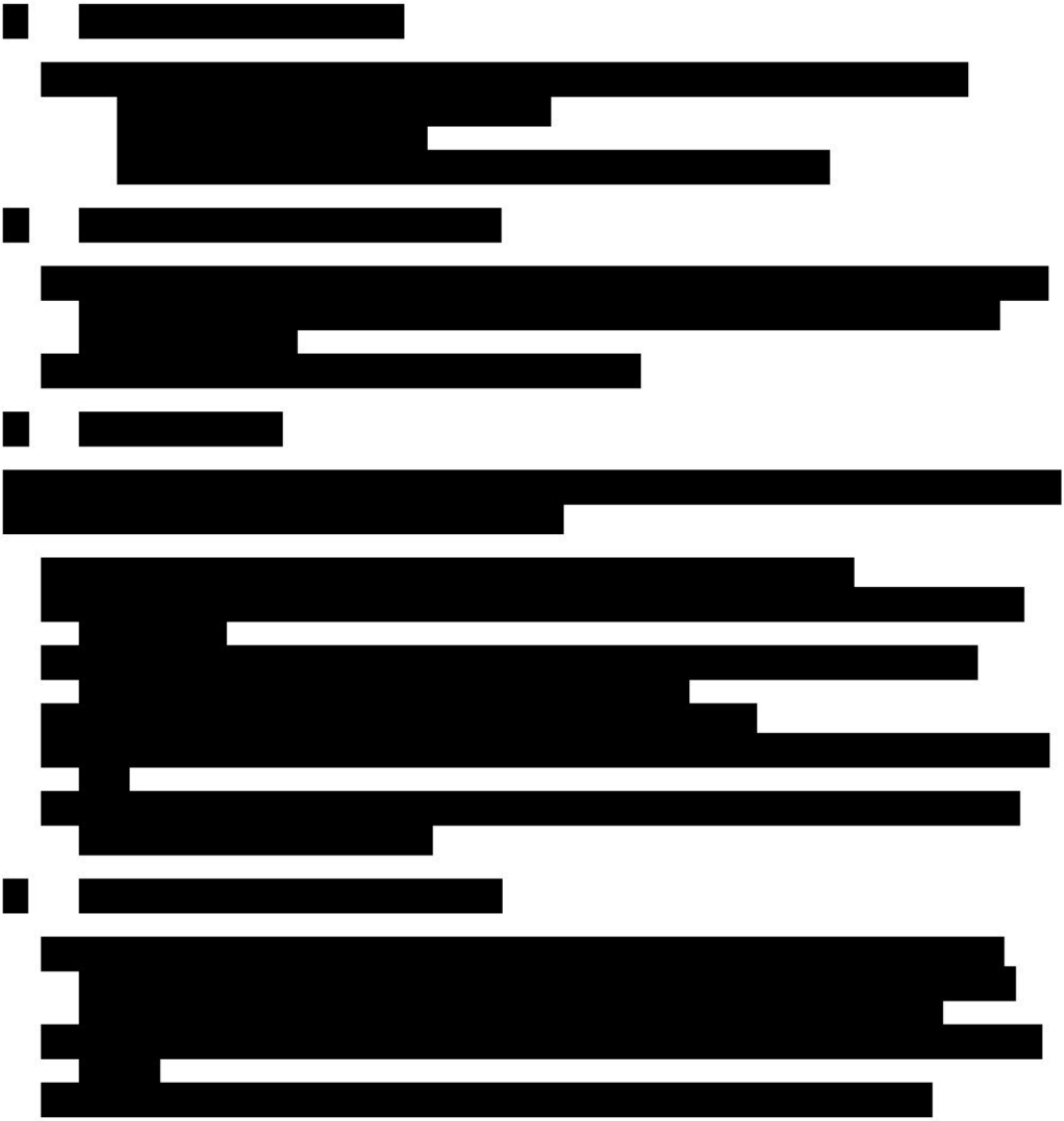
Site Principal Investigator: Manoj J. Raval, MD, MSc, FRCSC
Site Co-investigators: Carl J. Brown, MD, MSc, FRCSC
P. Terry Phang, MD, MSc, FRCSC, FACS, FABCRS
Ahmer Karimuddin, MD

Barts Health NHS Trust
Whitechapel
London E1 1BB, United Kingdom
Telephone: [redacted]
Site Principal Investigator: Charles Knowles,
Site Co-investigators: Ugo Grossi, MD, MBBChir, PhD, FRCS, FRCS
Mark Scott, BSc, PhD
Momotaz Sultana, BSc Hons, MBBS, MRCS, PGCert HE

APPENDIX F: Procedures for Monitoring Investigations

A. Selection of the monitor

Designated by the sponsor to oversee the investigation, the monitor must be an employee of the sponsor or an independent contractor or consultant. The monitor shall be qualified by training and experience to monitor the investigational study in accordance with all applicable regulations.



[redacted]