CLINICAL INVESTIGATION PLAN

Muscle Cell Mediated Therapy for Stress Urinary Incontinence in Males Following Prostate Surgery: An Investigation of Cook MyoSite Autologous Muscle Derived Cells

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

CLINICAL INVESTIGATION PLAN SIGNATURE PAGE

Global Sponsor Contact:

This clinical study will be conducted in accordance with the Clinical Investigation Plan (CIP), ICH GCP, 21 CFR 312, and other applicable requirements as appropriate. The CIP will be revised, as appropriate, based on new information.

CLINICAL INVESTIGATION PLAN SIGNATURE PAGE, CONTINUED

Principal 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.

CONFIDENTIALITY STATEMENT

This document shall be treated as a confidential document for the sole information and use of the clinical study team and the Institutional Review Board/Research Ethics Board IRB/REB.

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1.0 Clinical Investigation Plan Overview

This preliminary, prospective, single-arm clinical study will evaluate the safety and potential efficacy of Autologous Muscle Derived Cells for Urinary Sphincter Repair (AMDC-USR) for the treatment of male stress urinary incontinence (SUI) that develops following prostate surgery.

Prostate surgery can induce iatrogenic sphincter damage resulting in long-term SUI. Therefore, augmenting sphincter function may be beneficial to patients. Autologous muscle cell therapy, which involves isolation of cells from skeletal muscle biopsies, ex vivo expansion, and subsequent injection into the urethral sphincter, may serve as a potential durable therapy. In animal studies, muscle derived cells have successfully integrated within tissue to improve sphincter function. Intrasphincteric injection of AMDC-USR is expected to produce localized tissue changes near the injection site and is not expected to produce a systemic effect.

Patients will receive intrasphincteric injection of a single treatment of 150 x 10^6 AMDC-USR. For entrance into the study, patients must meet the study inclusion criteria and must not meet any of the exclusion criteria. Patients will have quantitative and qualitative measures of incontinence assessed before treatment and at various times after treatment.

The study will treat up to 30 patients at up to 5 clinical sites. Enrollment is expected to be completed within 2.5 years of initiating the study. Patients will be followed for 24 months post-treatment. The first 3 patients at each site must reach 1-month follow-up before subsequent patients can be treated at that site.

Male patients at least 18 years of age who have undergone prostate surgery at least 12 months prior to screening and who present with symptoms of SUI will be screened for eligibility for study participation. To participate, patients must meet all inclusion criteria and none of the exclusion criteria. Eligible patients will have muscle tissue harvested using a needle biopsy technique during an outpatient procedure. The harvested muscle tissue will be placed in a hypothermic medium and transported to the manufacturer for cell processing in their laboratory in Pittsburgh, PA (USA). The muscle derived cells (MDC) will be isolated and expanded in culture over several weeks to a final dose of 150 x 10^6 ± 20% AMDC-USR.

Due to the personalized nature of each autologous product, some products may not meet all

release specifications of purity and dose. If a product meets all predefined safety criteria, the product may be offered to the patient at the physician's discretion. Affected patients will be notified prior to their injection procedure and must provide consent of their willingness to receive an injection of product that does not meet all target criteria.

After reaching the desired concentration, the isolated and expanded AMDC-USR will be frozen and shipped back to the investigating physician. The physician will thaw the AMDC-USR and dilute the sample with an approximately equal volume of physiological saline. Under direct vision, the resulting suspension will be injected into the patient's urethral sphincter in a brief outpatient procedure.

Patients will be assessed for safety and improvement in urinary incontinence symptoms at 1, 3, 6 and 12 months following treatment. Adverse events will be assessed at all follow-up visits, as well as during follow-up calls at 1-2 days, 1 week, and 24 months. A study overview is depicted in Figure 1.1.

The primary safety measures will be the incidence of study product-related serious adverse events (SAEs) and the incidence of study product-related, biopsy procedure-related, and injection procedure-related adverse events and post-void residual (PVR) urine volume. Secondarily, potential efficacy will be evaluated based on reduction in the amount of urine leakage, as assessed by a 24-hour pad test at 1, 3, 6, and 12 months following treatment. Changes in patient-reported incontinence symptom severity, quality of life (QOL), and erectile dysfunction (ED) symptoms will also be assessed at 1, 3, 6, and 12 months following treatment.

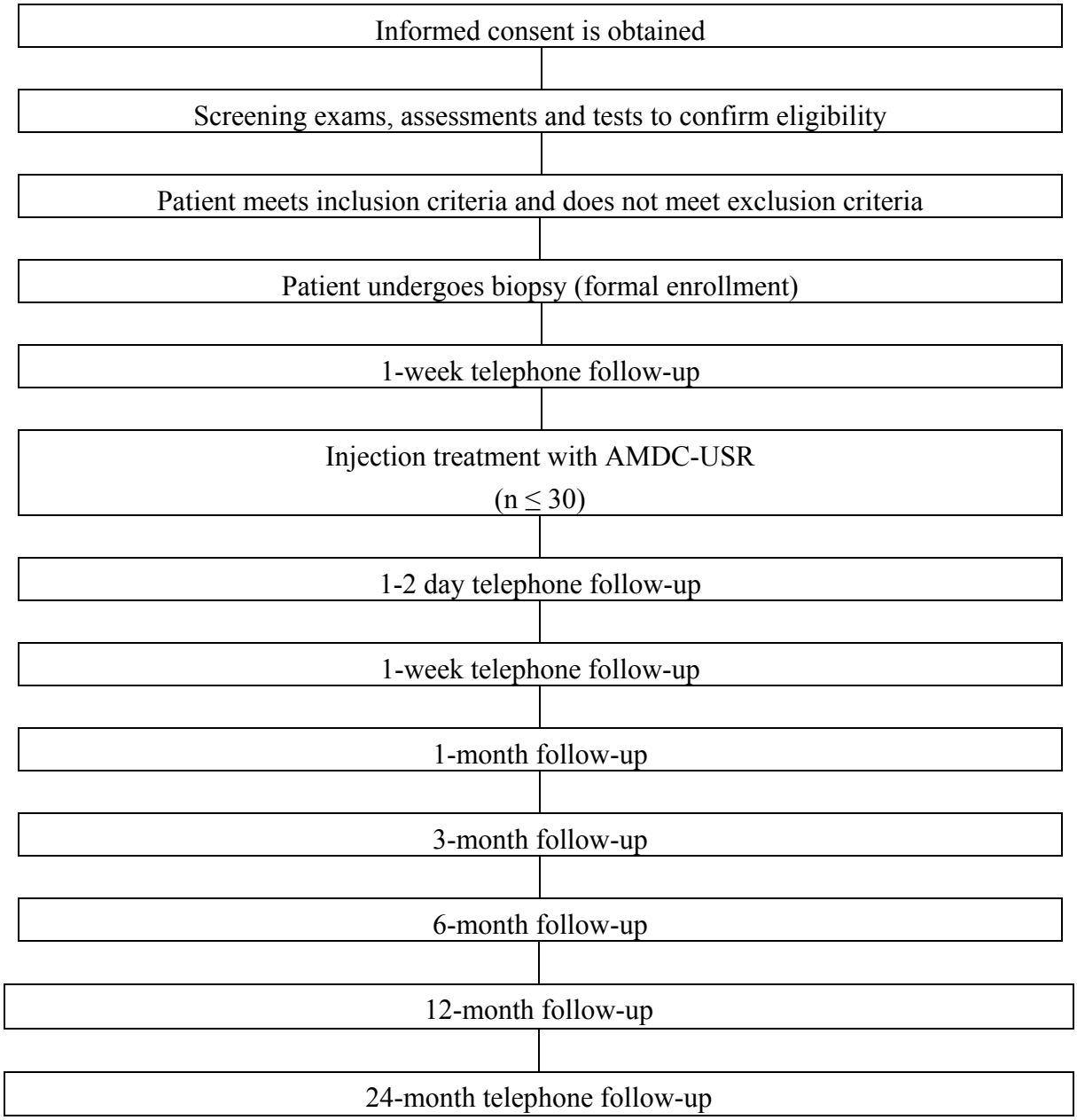

Figure 1.1. Study flow diagram

2.0 Objectives of the Clinical Study

2.1 Primary Objectives

The primary objective of this study is to evaluate the safety of AMDC-USR during the

24 months following treatment of SUI in male patients who have undergone prior prostate surgery.

Safety will be determined by the frequency and severity of adverse events related to study procedures and study product through 24 months following treatment of SUI in male patients who have undergone prior prostate surgery. PVR volume will be assessed through 12 months post-treatment to monitor potential retention or obstruction.

2.2 Secondary Objectives

In addition to the primary objective listed above, the following secondary objectives will be evaluated in this clinical study:

- Efficacy of AMDC-USR in the reduction of SUI symptoms at 1, 3, 6, and 12 months post-treatment
- Effect of AMDC-USR on QOL at 1, 3, 6, and 12 months post-treatment

Additionally, information on ED symptoms will be collected at 1, 3, 6, and 12 months post-treatment.

3.0 Product Description and Intended Use

3.1 General Product Description

Please reference the Investigator's Brochure for a detailed description of the product and dose to be used in the clinical study.

[redacted]

Cook MyoSite, Incorporated will perform cell processing and preparation of cell suspensions for study use in their cell processing facility in Pittsburgh, Pennsylvania (USA). Cell processing will begin with isolation of cells from the patient's tissue. The cells will then be grown in culture and

expanded in number. The culture process produces a final cell culture that is enriched in myogenic cell content. Cell culture will be performed in medium consisting of physiological saline solution with cell nutrients. Cell processing will follow current Good Manufacturing Practice (cGMP) methodologies to prevent contamination and to preserve tissue function and integrity. These practices will include defined procedures for tissue and cell handling, processing, and identification.

Each AMDC-USR study agent vial supplied to the clinical site will contain cryogenically preserved autologous muscle derived cells, prepared to ± 20% of the stated total viable cellular dose at the time of packaging, [redacted] Each study agent vial will be thawed at the clinical site prior to use and diluted with an approximately equal volume (2 mL) of injectable sodium chloride (saline) at physiological concentration, [redacted]

Materials contacting the patient's urethral tissue will include the patient's own muscle derived cells, the cryogenic medium in which the cells are suspended and shipped, and the physiological saline used to dilute the mixture for injection.

3.1.1 Dose Justification

A dose of 150 x 10^6 AMDC-USR was chosen [redacted]

Systemic adverse effects attributable to AMDC-USR have not been observed following intrasphincteric injection of AMDC in non-clinical[1] and clinical[2-4] studies. Therefore, delivery into the urethral sphincter of men is unlikely to produce systemic responses.

Because the risk to patients from adverse effects from the cells is expected to be the same as in other studies for sphincter-related indications, a dose with potential beneficial effect will be evaluated in the initial study.

3.2 Indication for Use

The AMDC-USR treatment is indicated for reduction in symptoms of urinary incontinence and improvement in patient QOL in men with stress urinary incontinence.

3.3 Product Identification and Tracking

Products under investigation will be tracked by the clinical site throughout the course of the study through the use of a product log, which includes information such as lot numbers, quantity, and disposition of products. Additionally, information such as the quantity and lot number(s) of products used in patients will be recorded on Case Report Forms (CRFs).

Each product is manufactured individually and labeled with a unique product code for identification and traceability. All cell preparations will be transported in identical vials with the same volume of transport medium and reconstituted to the same final volume prior to injection. Vials will be identified by a product code containing lot number, patient initials, and six unique digits. Additional procedures have also been established to ensure traceability.

3.4 Instructions for Use

The study procedure guidelines, which will be provided to physicians and appropriate study staff at the time of training, must be followed for step-by-step instructions for performing the following:

[1] Please reference the Investigator's Brochure, Section 5.3, Toxicology.

- Obtaining the muscle biopsy
- Packaging and shipping the muscle biopsy
- Complete instructions including storage and handling requirements
- Resuspending the final product (AMDC-USR)

Muscle Biopsy

The biopsy procedure will involve minor surgery to collect approximately 50-250 mg of the vastus lateralis muscle using a sampling needle. Prior to the biopsy, patients who are currently taking any form of anticoagulant medication must stop using the medication as per standard of care for outpatient surgery procedures. Antianxiety medication, analgesia, or minimal sedation may be provided according to each site's standard of care. [redacted]

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. The maximum permissible number of biopsy needle passes and the total number of biopsies is contingent upon patient tolerance and the satisfactory procurement of muscle tissue.

Using aseptic technique, the biopsy tissue will be transferred to the Biopsy Medium Vial. The Biopsy Medium Vial will be closed and packaged according to the study procedure guidelines for shipment to Cook MyoSite, Incorporated.

Dilution and Preparation for Injection

The frozen product will be thawed for at least 8-10 minutes at room temperature. The 2 mL of cell suspension will be diluted with 2 mL of physiological saline for an approximate total volume of 4 mL. The entire vial contents will be used for injection.

Cell Injection

The study agent (AMDC-USR) will be injected into the urethral sphincter. A course of prophylactic antibiotics will be given prior to the injection procedure. Ultrasound may be performed to aid in the injection procedure. Under direct vision, multiple injections will be

performed to circumferentially distribute AMDC-USR within the striated muscle of the urethral sphincter. Materials contacting the urethral tissue will include the patient's own AMDC-USR, the cryogenic medium in which the AMDC-USR are suspended and shipped, and the physiological saline used to dilute the mixture for injection. Prior to the injection, patients who are currently taking any form of anticoagulant medication must stop using the medication as per standard of care for outpatient surgery procedures. Antianxiety medication, analgesia, or minimal sedation may be provided according to each site's standard of care or physician's discretion.

After the injection is completed, the injected area will be examined for any excessive bleeding or excessive trauma. The patient will be asked to void, and an ultrasound/bladder scan will be performed to determine PVR urine volume.

4.0 Summary of Preliminary Studies

Please reference the Investigator's Brochure for a summary of non-clinical testing and a summary of previous clinical experiences with this product or similar products.

5.0 Risk Analysis and Risk Assessment

5.1 Risks and Foreseeable Adverse Events and Adverse Product Effects

Please reference the Investigator's Brochure for a list of specific risks of study procedures and study products.

5.2 Methods to Minimize Risks

Only trained healthcare professionals who are experienced with cystoscopy and urethral injection will administer this product. Patients will be selected according to the indication and in accordance with inclusion/exclusion criteria outlined in this document. Adherence to and training on the research clinical investigation plan (CIP) are necessary to reduce material- and procedure-related risks. Routine catheterization and venipuncture will be performed by qualified personnel.

The product design, non-clinical testing, clinical study design, and study procedure guidelines are intended to minimize the risks associated with the use of this product. The risks of the study have been minimized and the potential benefits outweigh the risks.

6.0 Design of the Clinical Study

6.1 Design of Study

This preliminary, prospective, single-arm clinical study will evaluate the safety and potential efficacy of AMDC-USR for the treatment of male SUI that develops following prostate surgery.

The study will treat up to 30 patients (treated with 150 x 10^6 AMDC-USR) at up to 5 clinical sites. Enrollment is expected to be completed within 2.5 years of initiating the study. Patients will be followed for 24 months post-treatment. The first 3 patients at each site must reach 1-month follow-up before subsequent patients can be treated at that site.

6.2 Inclusion and Exclusion Criteria

Patient eligibility for enrollment shall be based on known information at the time of the screening. Information obtained at a later date may contradict these criteria, but this will not be considered a deviation to the CIP.

Inclusion Criteria

A patient is deemed suitable for inclusion in the study if the patient meets the following criteria:

1. Male, at least 18 years old, with primary symptoms of SUI following prostate surgery that occurred at least 12 months prior to enrollment, as confirmed by medical history and clinical symptoms, including a focused incontinence evaluation.
2. Patient has undergone prostate surgery, such as radical prostatectomy or prostate resection, but has not undergone radiation therapy, cryotherapy, or high-intensity focused ultrasound of the prostate.
3. SUI severity must be ≥10 g and <400 g of urine leakage over 24 hours, as determined by a 24-hour pad test during screening. [2]

[2] Moore, et al.[5] suggest > 4 g as a minimum pad weight gain for incontinence in men, but that the upper limit for normal pad weight gain should be 8 g. Thus, > 8 g would be considered incontinence in men. Kumar, et al.[6] suggest > 400 g/24 h is high-grade incontinence (or total incontinence), and recommend men in this category receive an artificial urinary sphincter.

4. Patient has failed to achieve acceptable resolution of SUI symptoms following prior therapy.

Exclusion Criteria

A patient is excluded from enrollment into the study if any of the following are true:

Patient History-based Criteria:

1. Simultaneously participating in another investigational drug or device study or 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.
2. Previously treated with an investigational device, drug, or procedure for urinary incontinence within 6 months prior to signing consent.
3. Has ever been treated with a cell therapy for urinary tract dysfunction.
4. Has an artificial sphincter.
5. Previously treated with a periurethral balloon or adjustable sling for urinary incontinence.
6. Symptoms of stress urinary incontinence prior to prostate surgery.
7. Symptoms of only urge urinary incontinence as noted by basic evaluation of etiology from patient medical history, including a focused incontinence history.
8. Symptoms of overflow incontinence as noted by basic evaluation of etiology from patient medical history, including a focused incontinence history.
9. Symptoms of urinary incontinence in which stress urinary incontinence is not the predominant factor.
10. Routinely has more than 2 episodes of awakening to void during normal sleeping hours.
11. Urinary incontinence of neurogenic etiology or uncorrected congenital abnormality leading to urinary incontinence.
12. Indwelling urinary catheter or requires intermittent catheterization for bladder emptying.
13. Neuromuscular disorder (e.g., Parkinson's disease, muscular dystrophy, multiple sclerosis) that could lead to urinary incontinence.
14. Morbidly obese (BMI $\geq$ 35).
15. Uncontrolled diabetes.
16. Adult nocturnal enuresis.
17. Severe, chronic constipation.

18. Compromised immune system due to disease state, chronic corticosteroid use, or other immunosuppressive therapy.
19. History of pelvic organ radiation (e.g., brachytherapy, transurethral microwave therapy [TUMT], transurethral radiofrequency needle ablation [TUNA]).
20. History of high-intensity focused ultrasound (HIFU) treatment of the prostate.
21. History of cryotherapy treatment of the prostate.
22. Medical condition or disorder that may limit life expectancy or that may cause CIP deviations (e.g., unable to perform self-evaluations or accurately report medical history, urinary symptoms, or data).
23. History of bleeding diathesis or uncorrectable coagulopathy.
24. Known allergy or hypersensitivity to bovine proteins or allergens, gentamicin sulfate, or ampicillin that medically warrants exclusion as determined by the physician.
25. Unstable prostate-specific antigen (PSA) for 12 months as determined by the physician.
26. Any non-skin cancer that has necessitated treatment within the past 12 months.
27. Known history of abnormal detrusor activity.
28. Known history of adult vesicoureteral reflux.

Patient Physical Examination or Testing-based Criteria:

1. Does not have a viable mucosal lining along the urinary tract.
2. Current or history of fistula involving the urethra, bladder, or rectum.
3. Urethral stricture or bladder neck contracture requiring intervention to reopen (planned intervention or history of intervention)
4. Current or history of bladder stones.
5. Failure to produce a leak during the bladder stress test.
6. Moderate or severe urethral fibrosis at likely injection site.
7. Voiding difficulty (complains of difficulty emptying the bladder following ultrasound/bladder scan).
8. PVR urine volume $\geq$ 100 mL,[7] determined by ultrasound/bladder scan, after repeated testing (i.e., the patient was asked to revoid and the PVR volume was still $\geq$ 100 mL).
9. 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/or Syphilis.

Patient's Current Status-based Criteria:

1. If previously treated for prostate cancer, evidence of recurrent prostate cancer as determined by the physician during screening.
2. Does not use external collection device for SUI symptoms (e.g., pads, condom catheter, etc).
3. Cannot be, or is not willing to be, maintained on a stable dose or frequency of medication known to affect lower urinary tract function, including but not limited to, anticholinergics, beta 3 adrenergic receptor agonists, tricyclic antidepressants, SNRI or SSRI antidepressants, diuretics, or alpha-adrenergic blockers, or phosphodiesterase type-5 inhibitors, for at least 2 weeks prior to screening; or use of these medications is likely to change during the 12 months following treatment.
4. Cannot, or is not willing to, maintain the current treatment regimen for existing conservative therapy (e.g., pelvic floor muscle training routine, incontinence medications), excluding penile clamps.
5. Cannot, or is not willing to, stop use of penile clamp during the course of the study.
6. Requires prophylactic antibiotics for chronic urinary tract infections, cystitis, urethritis, prostatitis, orchitis, epididymitis, or balanitis, or has required 2 or more courses of antibiotics for lower urinary tract infections in the 2 months prior to signing consent.
7. Any condition, including current infection, which could lead to significant postoperative complications.
8. Current or acute conditions involving cystitis, urethritis, prostatitis, balanitis, orchitis, or epididymitis.
9. Refuses to provide written informed consent.
10. Not at least 18 years of age.
11. Not available for, or willing to comply, with the baseline and follow-up evaluations as required by the CIP.

6.3 Endpoints

6.3.1 Primary Endpoints

The primary safety endpoints include:

- Study product-related SAEs reported through 24-month follow-up;

- Study product-related, biopsy procedure-related, and injection procedure-related adverse events reported through 24-month follow-up; and
- PVR urine volume reported through 12-month follow-up.

6.3.2 Secondary Endpoints

The secondary endpoints include:

- Reduction in amount of urine leakage, as assessed by 24-hour pad test at 1, 3, 6 and 12 months post-treatment;
- Change in patient-reported incontinence symptom severity, as assessed by questionnaires at 1, 3, 6 and 12 months post-treatment; and
- Change in patient-reported QOL, as assessed by questionnaires at 1, 3, 6 and 12 months post-treatment.

Changes in ED symptoms will also be assessed at 1, 3, 6 and 12 months post-treatment.

6.3.3 Rationale for Endpoints

This is a preliminary study to assess the safety of intrasphincteric injection of AMDC-USR in male patients. Safety assessment will be based on the occurrence of product- and study procedure-related adverse events. Additionally, PVR volume will be assessed throughout the study to monitor potential retention or obstruction.

Efficacy measurements will be used in this study to assess the severity level of an individual's incontinence symptoms and the extent to which incontinence symptoms impair quality of life. Measures to assess incontinence include a 24-hour pad test, the International Consultation on Incontinence Questionnaire (ICIQ),[8,9] the Incontinence Quality of Life (IQOL) questionnaire,[9,10] the Patient Global Impression of Severity (PGI-S),[11,12] the Patient Global Impression of Improvement (PGI-I),[11,12] and the International Prostate Symptom Score (I-PSS).[13,14]

Since SUI and ED can be comorbidities that develop following prostate surgery, the 5-Item International Index of Erectile Function (IIEF-5)[15] questionnaire will be used to monitor symptoms of ED.

6.4 Variables to be Measured to Demonstrate Achievement of Endpoints

Safety endpoints will be measured as follows:

- Study product-related SAEs reported through 24-month follow-up;
- Study product-related, biopsy procedure-related, and injection procedure-related adverse events reported through 24-month follow-up; and
- Ultrasound/bladder scan determination of PVR volume on the day of injection and at 1, 3, 6 and 12 months post-treatment.

The secondary efficacy endpoints will be measured as follows:

- Reduction in amount of urine leakage from baseline as assessed by 24-hour pad test at 1, 3, 6 and 12 months;
- Change from baseline in patient-reported outcomes for incontinence symptom severity and QOL will be measured by ICIQ, IQOL score and subscores, I-PSS, and PGI-S score at 1, 3, 6 and 12 months; and
- Change in patient-reported incontinence symptom severity will also be measured by PGI-I score at 1, 3, 6 and 12 months.

In addition, change from baseline in patient symptoms of ED will be measured by the IIEF-5 questionnaire at 1, 3, 6 and 12 months. Patient clinical information including details of prior procedures for prostate surgery, underlying reason for prostate surgery, underlying disease severity, and any procedures or revisions following the incident procedure to address disease or SUI symptoms will be collected and evaluated as appropriate.

The clinical data will be collected on standardized Case Report Forms (CRFs). The schedule for assessments is summarized in Table 6.1.

Table 6.1. Data collection schedule

	Screening	**Biopsy**	**Post-biopsy**	**Treatment**	**Post-treatment**						
	Visit 1	**Visit 2**	**Phone**	**Visit 3**	**Phone**	**Phone**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Phone**
	Week 1-8[a]	**Week 2-10**	**Week 3-11**	**Day 0**	**Day 1-2**	**Week 1**	**Month 1**	**Month 3**	**Month 6**	**Month 12**	**Month 24**
Event	Screening	Biopsy	Follow-up	Injection	Follow-up	Follow-up	Office Visit	Office Visit	Office Visit	Office Visit	Follow-up
Informed Consent	X										
Inclusion/ Exclusion[b]	X										
Medical History	X										
Clinical Assessment	X						X	X	X	X	
Physical Examination	X										
Vital Signs	X										
Medication Log	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X			X			X	X	X	X	
Urine Culture[c]				X							
Bladder Stress Test	X									X	
24-hour Pad Test	X			X			X	X	X	X	
Post-void Residual Volume	X			X			X	X	X	X	
Questionnaires[d]: ICIQ, IQOL, PGI-S, I-PSS, IIEF-5	X			X			X	X	X	X	
Questionnaire[d]: PGI-I							X	X	X	X	
Blood Samples	X[f]						X			X	
Cystoscopy	X[e]			X						X	
Muscle Biopsy		X									
Injection				X							
Adverse Events	X	X	X	X	X	X	X	X	X	X	X
Telephone Follow-up			X		X	X					X

[a] It is recommended that screening tests conducted in Visit 1 be completed within 8 weeks preceding the biopsy visit.

[b] An electronic case report form system tracks inclusion/exclusion screening information.

[c] This test must be completed if the urinalysis is positive for nitrites or leukocyte esterase on the day of scheduled injection. Urine culture may also be performed at screening and at follow-up visits if nitrites or leukocyte esterase is detected by dipstick; however, urine culture is not required.

[d] Questionnaires will be collected in a paper format.

[e] An existing cystoscopy evaluation can be used if performed within 6 months prior to the time of consent.

[f] If the biopsy procedure is scheduled more than 30 days after the most recent bloodborne pathogen tests were completed, the bloodborne 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.

6.5 Measures to be Taken to Avoid or Minimize Bias

This preliminary, prospective, single-arm study is intended to collect information regarding the safety and potential efficacy of intrasphincteric injection of AMDC-USR for the treatment of male SUI that develops following prostate surgery. Study patients will be enrolled at up to 5 sites and uniform definitions will be used for study endpoints.

7.0 Methods

7.1 Patient Assessment and Screening

Male patients who present with SUI symptoms that developed following prostate surgery that occurred at least 12 months prior to enrollment may be considered for participation in this study.

7.2 Patient Consent

Patients who appear to meet the inclusion criterion and none of the exclusion criteria will be invited to participate in this study. All patients eligible for entry into the study will have the clinical study, as well as potential risks and benefits of their participation in the study, explained to them. Each patient who agrees to participate will be required to sign and date an informed consent document prior to any study-specific testing or procedure. If new information is obtained during the clinical study, any patient who has not exited the study will be informed about the new information, and will be reconsented at the discretion of the investigator or the site's IRB/REB.

7.3 Pre-enrollment (Visit 1) – Screening

Screening tests may be completed in up to 3 screening visits to accommodate site-specific scheduling. It is recommended that screening tests conducted in Visit 1 be completed within 8 weeks preceding the biopsy visit. Bloodborne pathogen testing must be completed within 30 days before the biopsy procedure. If more than one visit is required, adverse events that occur after the patient signs the consent form shall be recorded during subsequent visits.
After providing informed consent, the patient will have a medical history (including a urinary incontinence-focused history), a physical examination (including assessment of vital signs), a clinical assessment, and a medication assessment. Urine samples will be collected to test for nitrites and leukocyte esterase. If the urine test is positive for leukocyte esterase or nitrites, then a

urine culture may be performed. The patient will undergo a bladder stress test (please refer to Appendix A for the Instructions for the Bladder Stress Test) and will complete a 24-hour pad test. Patients will be instructed on how to perform the 24-hour pad test (please refer to Appendix B for the Instructions for the 24-Hour Pad Test) and will be provided with sufficient preweighed pads to complete the test. The completed 24-hour pad test must be returned before or at the next scheduled screening visit. A PVR urine volume will be measured with ultrasound/bladder scan. Patients will complete the following questionnaires: ICIQ, IQOL, PGI-S, I-PSS, and IIEF-5. Blood samples will be collected to assess for PSA levels, bloodborne pathogens, hematocrit, hemoglobin, WBC count, blood urea nitrogen (BUN) or urea, and creatinine. Patients will undergo cystoscopy for evaluation of the appearance of urethral and bladder tissue. An existing cystoscopy evaluation can be used if performed within 6 months prior to the time of consent. It is recommended that screening tests be performed from the least invasive test to the most invasive. Adverse events reported by the patient after informed consent is obtained will be recorded.

7.4 Point of Enrollment

Patients are considered enrolled in the study at the time of the biopsy procedure.

7.5 Medications

Patients may be given medication (including for pain or anxiety) according to each institution's standard of care or at the physician's discretion. Additionally, patients should be maintained on a stable dose or frequency of medication known to affect lower urinary tract function or erectile dysfunction, including but not limited to, anticholinergics, beta 3 adrenergic receptor agonists, tricyclic antidepressants, SNRI or SSRI antidepressants, diuretics, or alpha-adrenergic blockers, or phosphodiesterase type-5 inhibitors, for at least 2 weeks prior to screening assessments and throughout the study. A course of prophylactic antibiotics will be given prior to the injection procedure.

7.6 Biopsy (Visit 2)

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. 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. The maximum permissible number of

biopsy needle passes, and the total number of biopsies, is contingent upon patient tolerance and the satisfactory procurement of muscle tissue. If the biopsy procedure is scheduled for more than 30 days after the most recently completed bloodborne pathogen tests, the bloodborne 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. Additionally, the medication log will be updated if necessary. Any adverse events occurring since the last visit or before, during, or after the biopsy procedure will be recorded and reported as appropriate.

7.6.1 Post-Biopsy Follow-up (Phone)

Within 5 business days after the biopsy procedure, patients will be contacted by phone to determine whether any adverse events have occurred and whether any updates to the medication log are necessary.

7.7 Procedure (Visit 3) – Treatment Day 0

Approximately 12-13 weeks after the muscle biopsy, patients will return to the clinic for a brief outpatient procedure. At the start of the visit or before the visit, patients will provide a completed 24-hour pad test and complete the ICIQ, IQOL, PGI-S, I-PSS, IIEF-5 questionnaires. The 24-hour pad test and questionnaire data collected on the day of injection will be used as the baseline data. Prophylactic antibiotics will be given prior to the injection procedure. Prior to injection, patients will have a urine sample collected to test for nitrites and leukocyte esterase. If the urine test is positive for leukocyte esterase or nitrites, a urine culture must be performed and the injection will be delayed. A negative urine dipstick for leukocyte esterase and nitrites is required in order to undergo AMDC-USR injection. Ultrasound may be performed to aid in the injection procedure. Under direct vision, multiple injections will be performed to circumferentially distribute AMDC-USR within the striated muscle of the urethral sphincter. After the injection is completed, the injected area will be examined for any excessive bleeding or excessive trauma. Prior to discharge, patients will demonstrate a normal void and will have their PVR urine volume determined by ultrasound/bladder scan. The medication log will be updated if necessary. Any adverse events occurring since the last visit or before, during, or after the injection procedure will be recorded and reported as appropriate.

7.8 Follow-up

Follow-up windows are intended as recommendations only. They are not absolute and are not intended to limit data collection due to scheduling conflicts.

7.8.1 Post-Treatment Follow-up (Phone) – Treatment Day 1-2

Within 2 business days after treatment, patients will be contacted by phone to determine whether any adverse events have occurred and whether any updates to the medication log are necessary.

7.8.2 Post-Treatment Follow-up (Phone) – Treatment Week 1 Within five business days after treatment, patients will be contacted by phone to determine whether any adverse events have occurred and whether any updates to the medication log are necessary.

7.8.3 Follow-up (Visit 4) – Treatment Month 1 (± 1 week)

A clinical assessment will be performed. Patients will provide a completed 24-hour pad test, and will have a urine sample collected to test for nitrites and leukocyte esterase. If the urine test is positive for nitrites or leukocyte esterase, then it is recommended a urine culture be performed. Blood samples will be collected to assess PSA levels, hematocrit, hemoglobin, WBC count, BUN or urea, and creatinine. PVR urine volume will also be determined via ultrasound/bladder scan. If, after multiple void attempts, the PVR volume is ≥ 200 mL, additional evaluation for obstruction is recommended. During the visit, patients will complete the following questionnaires: ICIQ, IQOL, PGI-S, I-PSS, IIEF-5, and PGI-I. The medication log will be updated if necessary. Any adverse events occurring since the last contact will be recorded and reported as appropriate.

7.8.4 Follow-up (Visit 5) – Treatment Month 3 (± 1 week)

A clinical assessment will be performed. Patients will provide a completed 24-hour pad test, and will have a urine sample collected to test for nitrites and leukocyte esterase. If the urine test is positive for nitrites or leukocyte esterase, then it is recommended a urine culture be performed. PVR urine volume will also be determined via ultrasound/bladder scan. If, after multiple void attempts, the PVR volume is ≥ 200 mL, additional evaluation for obstruction is recommended. During the visit, patients will complete the following questionnaires: ICIQ, IQOL, PGI-S, I-PSS, IIEF-5, and PGI-I. The medication log will be updated if necessary. Any adverse events occurring since the last visit will be recorded and reported as appropriate.

7.8.5 Follow-up (Visit 6) – Treatment Month 6 (- 2, + 4 weeks)

A clinical assessment will be performed. Patients will provide a completed 24-hour pad test, and will have a urine sample collected to test for nitrites and leukocyte esterase. If the urine test is positive for nitrites or leukocyte esterase, then it is recommended a urine culture be performed. PVR urine volume will also be determined via ultrasound/bladder scan. If, after multiple void attempts, the PVR volume is ≥ 200 mL, additional evaluation for obstruction is recommended. During the visit, patients will complete the following questionnaires: ICIQ, IQOL, PGI-S, I-PSS, IIEF-5, and PGI-I. The medication log will be updated if necessary. Any adverse events occurring since the last visit will be recorded and reported as appropriate.

7.8.6 Follow-up (Visit 7) – Treatment Month 12 (- 2, + 4 weeks)

A clinical assessment will be performed. Patients will provide a completed 24-hour pad test, and will have a urine sample collected to test for nitrites and leukocyte esterase. If the urine test is positive for nitrites or leukocyte esterase, then it is recommended a urine culture be performed. Blood samples will be collected to assess PSA levels, hematocrit, hemoglobin, WBC count, BUN or urea, and creatinine. PVR urine volume will also be determined via ultrasound/bladder scan. If, after multiple void attempts, the PVR volume is ≥ 200 mL, additional evaluation for obstruction is recommended. The patient will undergo a bladder stress test and have a cystoscopy (for evaluation of the appearance of the urethral tissue). During the visit, patients will complete the following questionnaires: ICIQ, IQOL, PGI-S, I-PSS, IIEF-5, and PGI-I. The medication log will be updated if necessary. Any adverse events occurring since the last visit will be recorded and reported as appropriate.

7.8.7 Post-Treatment Follow-up (Phone) – Treatment Month 24 (-2, +4 weeks)

24 months after treatment, patients will be contacted by phone to determine whether any adverse events have occurred and whether any updates to the medication log are necessary.

7.9 Duration of Study and Patient Participation

Patients are expected to participate in this study for approximately 2.5 years from the time of the first screening visit. This duration includes time for screening, biopsy, injection, and 24 months of follow-up.

7.10 Criteria and Procedures for Withdrawal

A patient may decide to withdraw from the study at any time either before or after undergoing study procedures without prejudice or loss of care. The patient should notify the investigator of his desire to withdraw. The investigator will notify the sponsor. The investigator may also decide to withdraw a patient from the study at any time based on medical judgment. In all instances of withdrawal, data collected up to the time of patient withdrawal, including the study exit form and the appropriate study visit, shall be submitted to the data coordinating center and shall include the reason why the patient has been withdrawn from the study. Patients will be asked to allow access to their medical records for 30 days after the date of withdrawal. Any data collected on the patient up to the point of withdrawal plus 30 days may be used in the study.

In the event a patient cannot be contacted for post-treatment assessments, at least 3 attempts may be made to locate the patient, and these efforts will be documented. If the patient cannot be located, a lost to follow-up entry will be submitted.

7.11 Participation Endpoints of the Study

A patient's participation in the study will end after any of the following:

- Patient completed all scheduled clinical evaluations to 24 months;
- Patient withdrew or was lost to follow-up;
- Patient received nonstudy treatment for SUI (e.g., injection of a bulking agent or completed surgery for a sling);
- Study closed; or
- Patient died.

8.0 Statistical Considerations

8.1 Hypothesis to be Tested

This is a preliminary, prospective, single-arm study to assess the safety of AMDC-USR in males with SUI. The study is not powered statistically for any measurable outcomes.

8.2 Sample Size

The study will treat up to 30 patients at up to 5 clinical sites. Because this is a preliminary study, no formal statistical determination of sample size was performed.

8.3 General Analysis

Statistical analyses will be performed using SAS® for Windows® (release 9.3 or higher) or other widely accepted statistical software. Continuous variables will be reported as means and standard deviations unless otherwise noted. Categorical variables will be reported as percents. Ninety-five percent (95%) confidence intervals for all endpoint variables will be presented. Survival analysis techniques such as Kaplan-Meier or Cox Proportional Hazards may be incorporated if censoring of data occurs.

8.4 Missing Data

Missing data may be addressed using complete case analysis or multiple imputation.

8.5 Limitations of the Study

This preliminary study with a small sample size may limit the ability to generalize results to a larger population. The sample size is insufficient to allow definitive statements regarding efficacy. Patients will serve as their own controls with quantitative and qualitative measures of incontinence assessed before treatment and compared to the same measures at various times after treatment.

9.0 Deviations from Clinical Investigation Plan

Investigators are not allowed to deviate from this CIP without prior authorization by the sponsor except under emergency situations when necessary to preserve the rights, safety, or well-being of study patients.

Deviations and noncompliances will be recorded together with an explanation. Deviations or noncompliances that impact the rights, welfare, or safety of patients shall be reported to the sponsor and the IRB/REB as required and as soon as possible.

If appropriate, corrective and preventive actions will be discussed by the sponsor, investigator, or the IRB/REB to determine a suitable course of action.

10.0 Data Collection and Reporting

10.1 Electronic Case Report Forms

Patient data will be collected and entered by trained personnel at the clinical site into electronic Case Report Forms (eCRFs) through an electronic data capturing (EDC) system. This is a secure, web-based system, allowing those with permission to access data from any location at any time. Source data is to be retained for data entered into the EDC system. Data obtained and simultaneously entered into the EDC system may also serve as source documentation. Site personnel are required to undergo data entry training and will have unique login names and passwords in order to enter patient data. In accordance with 21 CFR Part 11, the EDC 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.

10.2 Data Reporting

Progress reports and a final report at the conclusion of the clinical study will be submitted by the investigators and sponsor to the regulatory authorities and IRB/REB as required by local regulations.

11.0 Data Management

11.1 Data Entry and Data Review

Each principal investigator or appropriately trained designee shall enter the clinical data into the EDC system on standardized CRFs. Investigators will provide all applicable clinical data and documentation to the sponsor. Patient data and documents pertaining to the study will be kept and archived by the sponsor. Data will be reviewed for missing data, data consistency, and reasonableness of responses. Discrepancies will be resolved through a formal query process involving direct contact with investigators or research coordinators. The data coordinating center is responsible for database management, data verification, data archiving, and data retention.

As needed to assist the sponsor in its research (e.g., during evaluation of an adverse event), data will be accessible to the sponsor, the participating investigators, the manufacturer, and companies or individuals the sponsor authorizes.

Cook Research Incorporated the data coordinating center, is physically located in the United States. Therefore, information collected within a country outside of the United States will be transmitted to the United States. Personal information will be protected by fair trade practices and in accordance with all applicable laws.

11.2 Data Monitoring Arrangements

The conduct of the clinical study will be supervised through a process of centralized and on-site monitoring. The data coordinating center will remotely monitor the study for data completeness and for adverse events. On-site monitoring will be implemented as necessary throughout the course of the study. The investigator/institution will provide direct access to source data/documents for study-related monitoring, audits, IRB/REB review, and regulatory inspection. Written procedures for monitoring the study are maintained by the data coordinating center and are summarized in Appendix C.

12.0 Procedures for Reporting Adverse Events

Adverse events are to be reported to the data coordinating center using the appropriate CRF. In cases of adverse drug reactions or SAEs, completed forms will be submitted to the data

coordinating center as soon as possible upon knowledge of the event. The data coordinating center will review the information submitted for possible reporting to the sponsor. Adverse events will be assessed in terms of relationship to product, relationship to biopsy procedure, relationship to injection procedure, severity, subsequent treatment/intervention required, and resolution status. Follow-up of all adverse events will be conducted per institutional standard of care.

The sponsor shall, if required according to applicable regulations, report the event to the appropriate regulatory authority. (Expedited reporting is required for serious and unexpected suspected adverse reactions [SUSARs].) If indicated, all principal investigators and clinical sites will be notified of applicable events by the sponsor. The principal investigator or designee will notify his/her IRB/REB of applicable events according to institutional guidelines.

13.0 Early Termination or Suspension of the Clinical Study

Any decision to suspend enrollment or terminate the clinical study, either completely or at one or more clinical sites, will be made by the sponsor and, if appropriate, the local IRB/REB. If a decision is made to terminate the study, all patients who have undergone one or more study procedures (i.e., biopsy or injection) will be followed for 30 days following the most recent procedure. Regulatory authorities or the IRB/REB will be notified as required by local regulations.

14.0 Ethical Considerations

This clinical study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and in accordance with 21 CFR 312 and ICH GCP.

The investigator is responsible for obtaining approval of this clinical study from the relevant IRB/REB at his/her associated institution. The clinical study will not begin until a favorable opinion of the IRB/REB has been obtained. The investigator is responsible for complying with requirements imposed by his/her IRB/REB or regulatory authority. Furthermore, the sponsor and the investigator will ensure that local regulations concerning data protection are followed.

15.0 Publication Policy

Publication policy, rights, and obligations for this study have been negotiated, detailed, and defined in the study's contractual documents with the clinical site and investigators.

16.0 Clinical Study Administration and Investigators

16.1 Approvals and Agreements

The sponsor and the principal investigators for each clinical 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 the signature page provided with this document.

16.2 Investigators

To see a complete list of the sponsor, manufacturer, monitor, and data coordinating center along with their contact information, please refer to Appendix D. A complete list of the principal investigators and coordinating investigators, along with their qualifications and contact information, will be updated and maintained by the data coordinating center. A list of the name and address of each reviewing IRB/REB will also be updated and maintained at the data coordinating center.

16.3 Insurance

Insurance for the study will be obtained by the sponsor prior to patient enrollment.

17.0 References

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

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9. Donovan J, Bosch, R., Gotoh, M., Jackson, S., Naughton, M., Radley, S., Valiquette, L., Batista, J.E., Avery, K. Symptom and Quality of Life Assessment. In: Abrams P, Cardozo, L., Khoury, S., Wein, A., ed. *Incontinence: Basics & Evaluation.* Vol 1: International Continence Society; 2005:519-584.
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11. Yalcin I, Bump RC. Validation of two global impression questionnaires for incontinence. *Am. J. Obstet. Gynecol.* 2003;189(1):98-101.
12. Viktrup L, Hayes RP, Wang P, Shen W. Construct validation of patient global impression of severity (PGI-S) and improvement (PGI-I) questionnaires in the treatment of men with lower urinary tract symptoms secondary to benign prostatic hyperplasia. *BMC Urol.* 2012; 12:30 doi: 10.1186/1471-2490-12-30. Epub 2012 Nov 7.
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14. AUA Practice Guideline Committee. AUA guideline on management of benign prostatic hyperplasia (2003). Chapter 1: Diagnosis and treatment recommendations. *J Urol.* 2003;170(2 Pt 1):530-547.
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APPENDIX A

Bladder Stress Test

All patients should have a bladder stress test as part of the screening procedures and at the 12-month follow-up. **Similar bladder fill volumes should be used for both tests.**

Bladder stress test

[redacted]

[redacted]

[redacted]

[redacted]

APPENDIX B

24-Hour Pad Test

All patients will have a 24-hour pad test as part of the screening procedures and at 1-month, 3-month, 6-month and 12-month follow-ups. The 24-hour pad test should be completed the day before each scheduled visit.

24-hour pad test

[redacted]

APPENDIX C

Written Procedures for Monitoring Studies

A. Selection of the monitor.

Designated by the sponsor to oversee the clinical study, the monitor may be an employee of Cook, an employee of a monitoring organization (CRO), or an independent contractor or consultant. The monitor shall be qualified by training and experience to monitor the study in accordance with all applicable regulations and standards for conducting clinical studies.

[redacted]

[redacted]

[redacted]

The monitor shall immediately notify the sponsor of any conditions of noncompliance with the CIP, conditions of the IRB/REB or regulatory authority approval, or the applicable regulations.

APPENDIX D

Contact Information

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

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

Data Coordinating Center and Monitor
Cook Research Incorporated
1 Geddes Way
West Lafayette, IN 47906 USA

Sponsor's Medical Expert
Oakland University William Beaumont School of Medicine
31157 Woodward Ave
Royal Oak, MI 48073-0996 USA

APPENDIX E

Definitions

Definitions for the following terms are not provided in this CIP, but can be found in the applicable regulations and guidances:

Adverse Events
Adverse Drug Reaction
Life-threatening Adverse Event or Life-threatening Suspected Adverse Reaction
Serious Adverse Event or Serious Suspected Adverse Reaction
Serious Adverse Drug Reaction
Serious and Unexpected Suspected Adverse Reaction
Suspected Adverse Reaction
Unexpected Adverse Event or Unexpected Suspected Adverse Reaction
Unexpected Adverse Drug Reaction