Solyx Protocol (U9915)

Cover Page

NCT01784588

A prospective, Non-randomized, Parallel Cohort, Multi-Center Study of the Solyx™ Single Incision Sling System Vs. The Obtryx II™ Sling System for the Treatment of Women with Stress Urinary Incontinence

Date Last Updated: August 22, 2018

Postmarket Study PS120093

Solyx™ Study

CLINICAL PROTOCOL

[redacted]

A Prospective, Non-Randomized, Parallel Cohort, Multi-center Study of the Solyx™ Single Incision Sling System vs. the Obtryx™ II Sling System for the Treatment of Women with Stress Urinary Incontinence

Sponsored By

Boston Scientific Corporation

[redacted]

Original Release: January 3, 2013

Current Version: August 22, 2018

[redacted]

[redacted]

2. Protocol Synopsis

Postmarket Solyx™ Study PS120093: A Prospective, Non-Randomized, Parallel Cohort, Multi-center Study of the Solyx™ Single Incision Sling System vs. the Obtryx™ II Sling System for the Treatment of Women with Stress Urinary Incontinence	
Objective(s)	The purpose of this study is to compare a single incision midurethral sling to a standard outside-in transobturator sling for the treatment of female stress urinary incontinence. It is hypothesized that the single incision sling will be non-inferior to the transobturator device in safety and effectiveness.
Test Device	Solyx™ Single Incision Sling System
Control Device	Standard outside-in transobturator sling (i.e. Obtryx™ II Sling System)
Study Design	Prospective, non-randomized, parallel cohort, multi-center study All study procedures will be standardized for uniformity. Physicians will have to document a minimum of ~10 procedures per device prior to participation in order to document competency and experience. Surgeons in the Obtryx cohort must complete a minimum of 5 Obtryx II cases to meet their case prerequisite obligation. [redacted] Concomitant procedures including pelvic floor repair can occur, per physician discretion. All concomitant procedures performed will be recorded. Subjects who undergo a medical intervention (surgical or non-surgical) to treat recurrence, persistence of SUI, or a mesh complication will be followed to 36 months from the initial study procedure.
Planned Number of Subjects	Assuming 20% lost to follow-up at 36 months, approximately 280 subjects (140 in each study arm) are planned
Planned Number of Centers / Countries	Up to 30 study centers

Postmarket Solyx™ Study PS120093: A Prospective, Non-Randomized, Parallel Cohort, Multi-center Study of the Solyx™ Single Incision Sling System vs. the Obtryx™ II Sling System for the Treatment of Women with Stress Urinary Incontinence	
Primary Endpoint	The primary endpoint is an assessment of improvement in stress urinary incontinence at 36 months as compared to Baseline, by a composite of objective and subjective measures: negative cough stress test with protocol required bladder fill procedure and a subject self-reported improvement in their condition, through the Patient Global Impression of Improvement (PGI-I).
[redacted]	[redacted]
Method of Assigning Subjects to Treatment	This study is a non-randomized, parallel cohort study. Physicians and study centers will be selected based on their device experience and will be device-specific centers (i.e. Solyx™ or Obtryx II™ subjects only). Approximately 140 subjects will be enrolled in each respective cohort.
Follow-up Schedule	Study follow-up duration is for 3 years from primary study procedure: • Screening/Enrollment Visit • Pre-operative/Baseline Visit • Surgery and Discharge

Postmarket Solyx™ Study PS120093: A Prospective, Non-Randomized, Parallel Cohort, Multi-center Study of the Solyx™ Single Incision Sling System vs. the Obtryx™ II Sling System for the Treatment of Women with Stress Urinary Incontinence	
	• Week 2 Visit • Week 6 Visit • Month 6 Visit • Month 12 Visit • Month 18 Visit • Month 24 Visit • Month 36 Visit (End of study)
Study Duration	Approximately 3 years from last subject enrolled
Key Inclusion Criteria	1. Female ≥ 18 years of age 2. Willing and able to comply with the study procedures and provide written informed consent to participate in the study (subject or legal representative) 3. Diagnosed with predominant SUI confirmed by positive cough stress test during the protocol required bladder fill procedure (see manual of operations) 4. Confirmed SUI is greater than urge incontinence with MESA 5. Cystometric capacity ≥ 300 cc 6. Post-void residual (PVR) of < 150 cc 7. Medically approved for general, regional or monitored anesthesia

Postmarket Solyx™ Study PS120093: A Prospective, Non-Randomized, Parallel Cohort, Multi-center Study of the Solyx™ Single Incision Sling System vs. the Obtryx™ II Sling System for the Treatment of Women with Stress Urinary Incontinence	
Key Exclusion Criteria	1. Subjects who are pregnant, lactating, or planning future pregnancies 2. Subjects with a chief complaint of overactive bladder 3. Subjects with a pattern of recurrent urinary tract infections, defined as ≥ 2 culture-proven urinary tract infections during a 6-month period prior to surgery or ≥ 3 in a 12-month period 4. Subjects with previous surgical procedures for SUI including bulking, urethral sling, bone anchor, Burch procedure, pubo-vaginal sling, and MMK procedure. Previous surgical procedures for SUI does not include Kelly plication, Botox, anterior repair, or Inter-Stim. 5. Subjects with prior pelvic organ prolapse surgery who experienced mesh complications 6. Subjects with previous radiation therapy to the pelvis 7. Subjects with known or suspected hypersensitivity to polypropylene mesh 8. Subjects with any of the following confounding conditions: a. Neurogenic bladder b. Urethral stricture and bladder neck contracture c. Bladder stones or tumors d. Urinary tract fistula or diverticula e. Pathology which would compromise implant placement including subjects currently taking anticoagulation therapy f. Pathology that would limit blood supply or infections that would compromise healing including chemotherapy, systemic steroids and systemic immunosuppressants 9. Subjects with diabetes and an A1c ≥ 7% 10. Non-English speaking subjects 11. Subjects who have participated in an investigational study (medical device or drug) within 30 days of study entry that may impact analysis of this device or have previously participated in the current study

Postmarket Solyx™ Study PS120093: A Prospective, Non-Randomized, Parallel Cohort, Multi-center Study of the Solyx™ Single Incision Sling System vs. the Obtryx™ II Sling System for the Treatment of Women with Stress Urinary Incontinence	
Primary Statistical Hypothesis	The single incision sling will be non-inferior to the standard outside-in transobturator sling for the treatment of female stress urinary incontinence in safety and effectiveness at 36 months as compared to Baseline. Statistical testing will be performed to determine if success rate of improvement in stress urinary incontinence at 36 months of single incision sling (treatment) group will be non-inferior to transobturator device (control) group. The null hypothesis is that the success rate in treatment group is less than or equal to the success rate in control group minus margin: $Ho: \pi_{treatment} - \pi_{control} \leq -\Delta$ The alternative hypothesis is: $Ha: \pi_{treatment} - \pi_{control} > -\Delta$ where $\pi_{treatment}$ and $\pi_{control}$ are the success rate of improvement in stress urinary incontinence at 36 months in treatment group and control group respectively, and Δ is defined as the non-inferiority margin.

Postmarket Solyx™ Study PS120093: A Prospective, Non-Randomized, Parallel Cohort, Multi-center Study of the Solyx™ Single Incision Sling System vs. the Obtryx™ II Sling System for the Treatment of Women with Stress Urinary Incontinence	
Statistical Test Method	For each of the primary endpoint and serious adverse events, non-inferiority of the single-incision sling will be evaluated using a two-sided 90% confidence interval for the treatment difference (single-incision minus transobturator). The confidence interval will be calculated based on the pooling of treatment differences across propensity score strata. All statistical analyses will be performed by the Sponsor per the Statistical Analysis Plan. [redacted]
[redacted]	[redacted]

3. Table of Contents

[redacted]

[redacted]

3.2. *Table of Tables*

[redacted]

4. Introduction

The prevalence of urinary incontinence in adult women is estimated at 4%-35%.[1] It is considered severe in about 3%-17% of adult women. Urinary incontinence is considered a "potentially debilitating social problem which leads to high health care costs." [2] The most common surgery for stress urinary incontinence (SUI) is the minimally invasive sling surgery which has replaced the Burch colposuspension as gold standard treatment for female urinary stress incontinence.[3] Incontinence surgery has become a routine part of urologic care but often can be difficult to manage complications and recurrent incontinence.[4]

Mid-urethral slings have been reported in published literature to be highly efficacious in managing SUI in women. The transobturator placement was developed to decrease morbidity, but has been noted to be associated with a higher incidence of thigh pain than the retropubic approach. Single incision slings were developed to offer the benefits of the transobturator approach in addition to a minimally invasive approach through a single 1.5 cm incision to the vagina and without exiting the skin.

[redacted]

5. Device Description

The Solyx™ SIS (Single Incision Sling) System is a sterile single use system consisting of one (1) delivery device and one (1) mesh assembly. The mesh assembly is comprised of a polypropylene knitted mesh with polypropylene carriers at each end of the distal mesh. The carrier is designed to be placed on the tip of the delivery device. The disposable delivery device consists of a handle, a [redacted] shaft and a deployment mechanism. The delivery device is designed to facilitate the passage of the mesh assembly through bodily tissues for placement into the obturator internus muscle.

The Obtryx™ II System is a sterile, single use system consisting of two (2) delivery devices and one (1) mesh assembly. The mesh assembly is comprised of a polypropylene knitted mesh with dilator legs and a center tab. At the distal ends of the dilator legs there are association loops designed to be placed in the needle slot of the distal end of the delivery device. The disposable delivery device consists of a handle with a [redacted] needle. The needle is designed to facilitate the passage of the mesh assembly through bodily tissues for placement through the obturator foramen.

6. Objectives

The primary objective is to evaluate clinical effectiveness of the single incision sling.
[redacted]

7. Endpoints

Primary Endpoint

The primary endpoint of the study is an assessment of improvement in stress urinary incontinence at 36 months as compared to Baseline by a composite of objective and subject measures: negative cough stress test with protocol required bladder fill procedure (see manual of operations) and a subject self-reported improvement in their condition through the Patient Global Impression of Improvement (PGI-I).

[redacted]

[redacted]

8. Design

This study is a prospective, non-randomized, parallel cohort, multi-center study.

The final primary endpoint will be assessed once all subjects have completed the 36 month study visit. All subjects will be followed to month 36 or until study completion if discontinued prior to month 36. All study procedures will be standardized for uniformity.

[redacted]

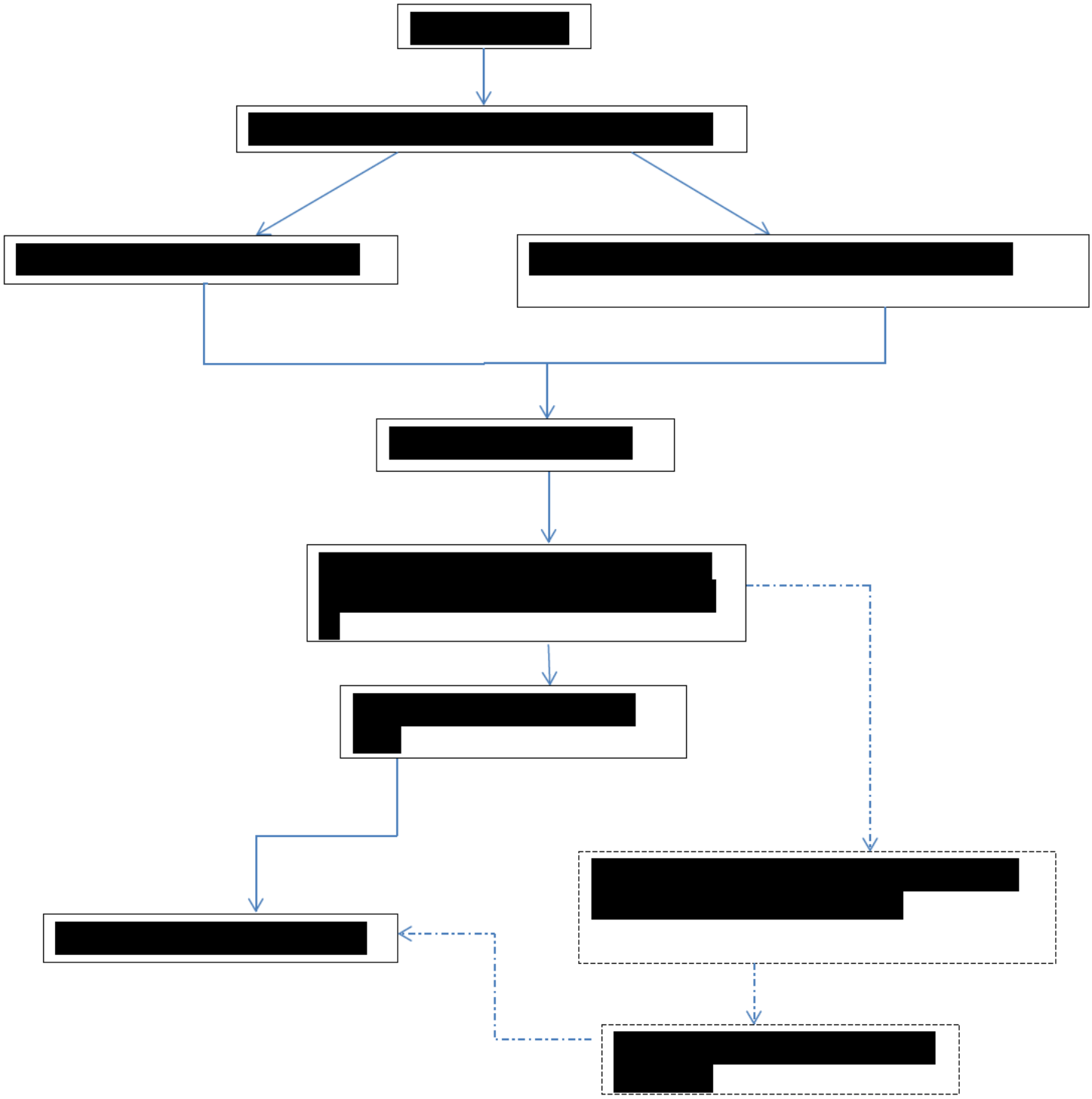
8.1. *Scale and Duration*

The study will be conducted at up to 30 sites at a rate of approximately 4 subjects per site per month.

[redacted]

Once enrolled into the study, subjects will be followed to 36 months post-surgery to be evaluated for the primary endpoint analysis. The total duration of each subject's participation in the study is 36 months from study procedure.

Subjects who undergo a medical intervention (surgical or non-surgical) to treat recurrence, persistence of SUI, or a mesh complication will be followed to 36 months, post the initial study procedure.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8.2. *Treatment Assignment*

This post-approval study is a non-randomized, prospective, parallel cohort study across multiple centers. Subjects will be screened against the study Inclusion/Exclusion criteria and if eligible, enrolled into the study after providing Informed Consent. Approximately 140 subjects will receive the Solyx Sling System as the treatment group, and 140 subjects will receive the Obtryx II Sling System as the control group across the entire study.

To reduce selection bias in this non-randomized study, each study center will be permitted to enroll subjects in only one of the treatment groups. Physicians will be selected based on device and clinical research experience and will decide which device to implant in subjects prior to study initiation at their center. This decision will be documented. All subjects meeting the eligibility criteria at the study center will be screened and enrolled, as applicable. [redacted]. Furthermore, at study completion and final data analysis, a comparison of baseline characteristics of patients in the two groups will occur and, if necessary, statistical adjustments performed to control for baseline differences.

Should one study-wide arm reach 140 subjects prior to the other, enrollment will be capped in that arm and the other study arm will remain open to enrollment until it also reaches 140 subjects. Those study centers enrolling the device arm that have met enrollment capacity will be closed, per Sponsor discretion.

8.2.1. Treatment and Control

The treatment device in this study is the Solyx Single Incision Sling System and the control device in this study is the Obtryx II Sling System. Please refer to the Directions for Use document for device-specific information.

9. Subject Selection

9.1. *Study Population and Eligibility*

This study will enroll adult English-speaking women, who are not pregnant or planning future pregnancies, have been diagnosed with predominant stress urinary incontinence and

who will undergo the surgical placement of a sling as treatment, who may or may not also undergo a concomitant procedure (such as pelvic floor prolapse repair).

To assess for eligibility for this study, inclusion and exclusion criteria are included in Sections 9.2 and 9.3 below.

9.2. *Inclusion Criteria*

Subjects who meet all of the following criteria may be given consideration for inclusion in this clinical investigation, provided no exclusion criterion (see Section 9.3) is met.

1. Female ≥ 18 years of age
2. Willing and able to comply with the study procedures and provide written informed consent to participate in the study (subject or legal representative)
3. Diagnosed with predominant SUI confirmed by positive cough stress test during the protocol required bladder fill procedure (see manual of operations)
4. Confirmed SUI is greater than urge incontinence with MESA
5. Cystometric capacity ≥ 300 cc
6. Post-void residual (PVR) of ≤ 150 cc
7. Medically approved for general, regional or monitored anesthesia

9.3. *Exclusion Criteria*

Subjects who meet any one of the following criteria will be excluded from this clinical study.

1. Subjects who are pregnant, lactating, or planning future pregnancies
2. Subjects with a chief complaint of overactive bladder
3. Subjects with a pattern of recurrent urinary tract infections, defined as ≥ 2 culture-proven urinary tract infections during a 6-month period prior to surgery or ≥ 3 in a 12-month period
4. Subjects with previous surgical procedures for SUI including bulking, urethral sling, bone anchor, Burch procedure, pubo-vaginal sling, and MMK procedure. Excluding Kelly plication, Botox, anterior repair, or Inter-Stim
5. Subjects with prior pelvic organ prolapse surgery who experienced mesh complications
6. Subjects with previous radiation therapy to the pelvis
7. Subjects with known or suspected hypersensitivity to polypropylene mesh
8. Subjects with any of the following confounding conditions:
    a. Neurogenic bladder
    b. Urethral stricture and bladder neck contracture

c. Bladder stones or tumors

d. Urinary tract fistula or diverticula

e. Pathology which would compromise implant placement including subjects currently taking anticoagulation therapy

f. Pathology that would limit blood supply or infections that would compromise healing including chemotherapy, systemic steroids and systemic immunosuppressants

9. Subjects with diabetes and an A1c ≥ 7%

10. Non-English speaking subjects

11. Subjects who have participated in an investigational study (medical device or drug) within 30 days of study entry that may impact analysis of this device or have previously participated in the current study

10. Subject Accountability

10.1. *Point of Enrollment*

Subjects will be considered enrolled once they have been determined to be eligible against all inclusion and exclusion criteria and have signed Informed Consent. Subjects will be considered Intent-to-Treat (ITT) once the sling procedure has been initiated (i.e. anesthesia administered). All enrolled subjects will be assigned to receive either the treatment or control device by the Investigator prior to the site initiation as sites will be device-specific centers. All ITT subjects who receive the assigned device and have no major protocol deviations will be considered part of the Per Protocol analysis.

10.2. *Withdrawal*

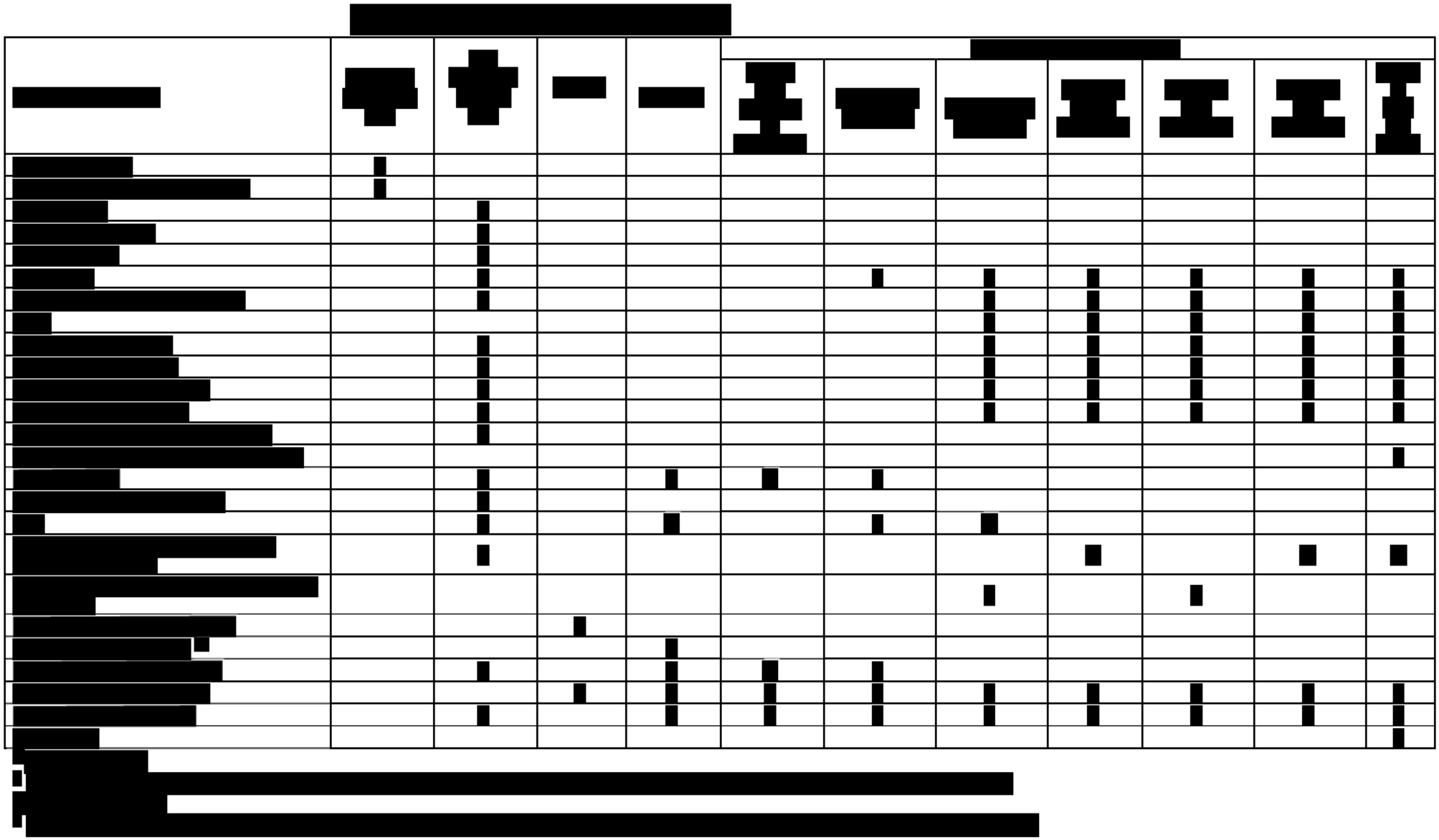
All subjects enrolled in the clinical study (including those withdrawn from the clinical study or lost to follow-up) will be accounted for and documented. If a subject withdraws from the clinical investigation, the reason(s) will be recorded.

Reasons for study withdrawal may include, withdrawn consent, lost to follow-up, subject death or other reasons to be documented on the Case Report Form.

Once a subject withdraws from the study, the Case Report Form will be completed as appropriate up to the point of withdrawal and all Adverse Events shall be closed or documented as appropriate. Withdrawn subjects will be included in the ITT analysis and will not be replaced.

11. Study Methods

[redacted]



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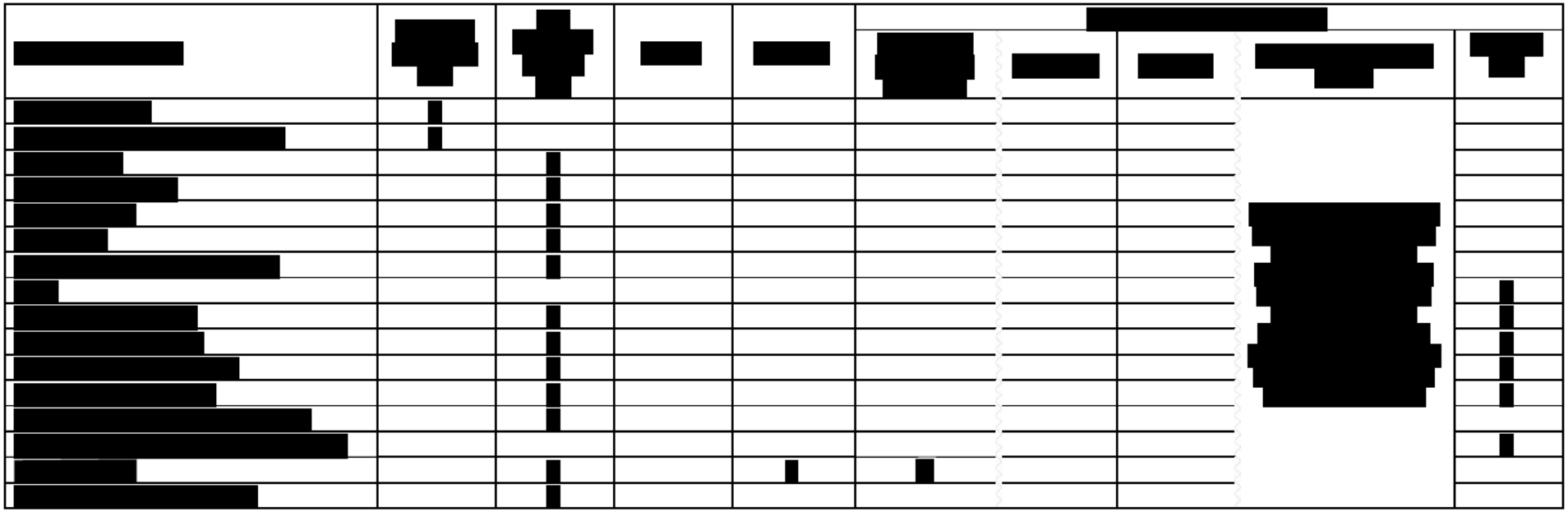

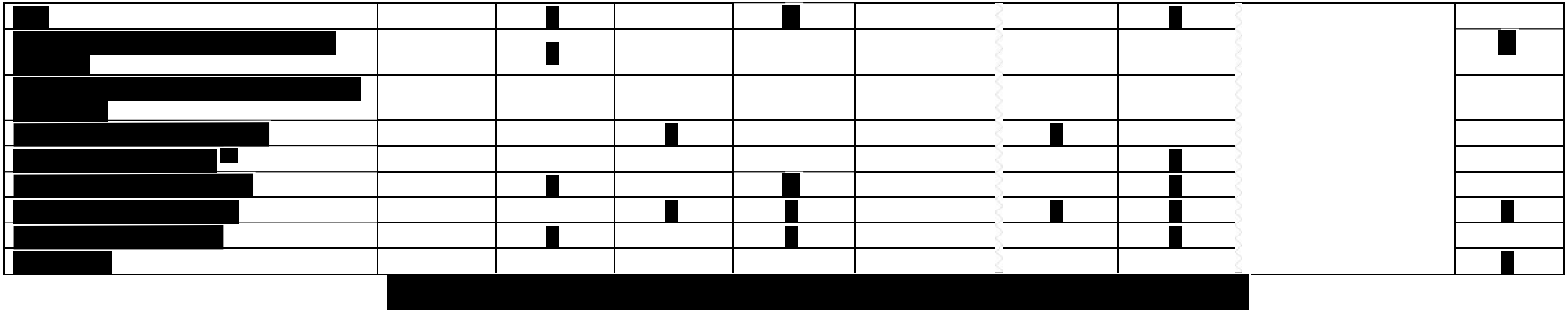

11.2. *Study Candidate Screening*

Potential subjects will be identified by qualified staff at each selected study center as per their individual processes that will be documented at either the Site Qualification Visit and/or the Site Initiation Visit. As previously noted, study centers will enroll subjects in one of the two treatment groups.

Subjects will be screened against the inclusion and exclusion criteria and, if confirmed to meet all requirements will be eligible to be consented for Intent-to-Treat.

Subjects who do not meet the inclusion and exclusion criteria are not ITT and are considered screening failures. Information on screening failure subjects will be captured in the source documentation and screening logs and will include reasons for screen failure.

11.3. *Informed Consent*

Prior to any study-related assessments being performed, each subject (and legally authorized representative, as applicable) must sign an Institutional Review Board (IRB) approved informed consent document to participate in the study as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form will describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information.

The subject or legally authorized representative will be given ample opportunity to inquire about details of the study to decide whether or not to participate in the study. Copies of the informed consent form will be provided to the subject and original documents filed at each study center as per regulatory requirements.

[redacted]

[redacted]

[redacted]

[redacted]

11.5. *Study Completion*

All subjects who have completed the study surgery and discharge will proceed to follow-up through the above-outlined study visits to Month 36 where the primary endpoint analysis will be assessed. The study will be considered complete when the last subject completes this visit. All subjects completing the Month 36 visit will be considered complete.

11.6. *Re-Intervention*

It is the intention of this study to demonstrate an improvement in stress urinary incontinence through clinical effectiveness of a single incision sling. However, it is recognized that during the course of the study, there is a possibility subjects may require a re-intervention for events including but not limited to failed sling repair, persistence of SUI symptoms, or a mesh-related complication. A re-intervention may include surgical or non-surgical treatments (medical). For the purpose of this study surgical interventions shall be classified as "re-surgery" and non-surgical interventions shall be classified as "re-interventions".

Non-surgical interventions (re-interventions) are defined as office-based procedures and do not involve an operating room procedure. Examples of non-surgical interventions may include but are not limited to an office visit to trim exposed mesh in the vagina or physical therapy to treat procedural complications or persistent SUI symptoms. Data on non-surgical interventions will be captured in the CRFs. Subjects will continue to be followed per the regular study visit schedule.

Surgical interventions (re-surgery) are surgical operations or procedures performed to correct recurring SUI symptoms or a mesh-related complication. These surgical events typically may occur on an outpatient basis yet can require admission to a hospital. Surgical events may include a re-operation to remove mesh material or to loosen the sling as well as a bulking agent application to treat recurrence. The decision to perform a re-surgery will be per physician and subject discretion and all re-surgery data will be captured in the Case Report Forms. Subjects undergoing re-surgery to treat recurrence or persistence of SUI symptoms are considered treatment failures.

Subjects undergoing a re-surgery will be followed to 36 months post their initial study procedure as indicated in [redacted] The subject should return to the clinic for the next regular study visit as per the adjusted schedule. If the subject elects to not undergo re-surgery, then the subject will be followed to the Month 36 visit unless the subject chooses to withdraw consent from the study. No subject will be followed for more than 36 months beyond their initial study procedure.

11.7. *Subject Death*

In the event of a subject death, results are to be documented in the source documentation and Case Report Form and reported to the Sponsor within the timeframe noted in Table 21.4-1: Investigator Reporting Requirements. If an autopsy is conducted, a copy of the final autopsy

report should be submitted to the Sponsor or designee. The primary objective of the autopsy is to determine the cause of death, complications, and other relevant findings.

12. Statistical Considerations

12.1. *Endpoints*

12.1.1. Primary Endpoint

The primary endpoint is an assessment of improvement in stress urinary incontinence at 36 months as compared to Baseline.

12.1.1.1. Hypotheses

Statistical testing will be performed to determine if the single incision sling (treatment) is non-inferior to the transobturator device (control). The null hypothesis is that the success rate in treatment group is less than or equal to the success rate in control group minus margin:

$$Ho: \pi_{treatment} - \pi_{control} \leq -\Delta$$

The alternative hypothesis is:

$$Ha: \pi_{treatment} - \pi_{control} > -\Delta$$

where $\pi_{treatment}$ and $\pi_{control}$ are the success rate of improvement in stress urinary incontinence at 36 months in treatment group and control group respectively, and Δ is defined as the non-inferiority margin.

12.1.1.2. Sample Size

Statistical power calculation is based on a non-inferiority assumption with a binary outcome. [redacted]

12.1.1.3. Statistical Methods

Non-inferiority will be evaluated using a two-sided 90% confidence interval for the treatment difference (single-incision minus transobturator). If the entire confidence interval is above -15%, non-inferiority will be demonstrated. The confidence interval will be calculated based on the pooling of treatment differences across propensity score strata for a binary endpoint, as described in Section 12.3.

Subjects with missing data will be considered treatment failures. As a sensitivity analysis, non-inferiority will be evaluated using only the subjects for whom the endpoint was assessed, i.e., available-case analysis.

[redacted]

[redacted]

[redacted]

12.2. *General Statistical Methods*

12.2.1. Analysis Sets

The Intent-to-Treat (ITT) subject population includes all subjects who provide written informed consent to be enrolled into the study, met all eligibility criteria, and have a surgery initiated (i.e. anesthesia administered).

The Treated Population includes all subjects who undergo the study surgical procedure. The subject is defined to have successfully completed the surgical procedure (i.e. sling placement successful) and discharged.

The Per Protocol (PP) population includes all subjects in the ITT Population who received the assigned treatment and had no major protocol deviations. All primary [redacted] analyses will be performed on both the ITT and per-protocol populations, with ITT considered the main analysis and per protocol as a sensitivity analysis. The analyses will include only the available cases, unless specified otherwise.

12.2.2. Control of Systematic Error/Bias

To reduce selection bias in this non-randomized study, each study center will be permitted to enroll subjects in only one of the treatment groups. Physicians will be selected based on device and clinical research experience and will decide which device to implant in subjects prior to study initiation at their center. This decision will be documented. All subjects meeting the eligibility criteria at the study center will be screened and enrolled, as applicable. Imbalance between the treatment arms at baseline is a potential source of bias. To facilitate an unbiased treatment comparison, the analyses of outcomes will be based on stratification on the propensity score, as described in Section 12.3. The propensity score will be calculated from only baseline data prior to performing any analysis of endpoints, in order to avoid introducing bias from knowledge of outcome data.

[redacted]

[redacted]

[redacted]

12.3. ***Data Analyses***

Analyses comparing the treatment groups will be adjusted for the propensity score. [redacted]

[redacted]

[redacted]

12.3.2. Interim Analyses

No formal interim analysis is planned. [redacted]

12.3.3. Justification of Pooling

For each group, the analyses will be presented using pooled data across institutions. An analysis of the poolability will be made using logistic regression , with the primary endpoint as the response, fixed effects for treatment arm and propensity stratum, and a random effect for study center, to assess differences between study institutions and to justify pooling data across institutions.

[redacted]

12.3.5. Changes to Planned Analyses

Any changes to the planned statistical analyses made will be documented in an amended Statistical Analysis Plan. Changes from the planned statistical methods will be documented in the clinical study report along with a reason for the deviation.

13. Data Management

13.1. *Data Collection, Processing, and Review*

Good Clinical Practice Guidelines require that investigators maintain information in the subject's medical records, laboratory reports, clinic charts that correspond to data recorded on the Case Report Forms. In order to comply with these requirements, the following information should be maintained as source documentation, including but not limited to:

- Medical history/physical condition of the subject before enrollment
- Protocol entry criteria
- Dated and signed notes for specific results of procedures and exams
- Laboratory reports
- Information related to adverse events
- Re-interventions (including physical therapy, bulking, mesh trimming)
- Surgical notes, including subject condition and re-surgery if applicable
- Quality of life assessments and VAS pain scales
- Discharge Summaries/Procedure reports
- Autopsy reports

Subject data will be recorded on Case Report Forms which will be provided by the Sponsor or designated vendor. The data reported on the Case Report Forms shall be derived from source documentation and shall be consistent with these source documents. Any discrepancies shall be explained and documented. Any change or correction made to the clinical data will be dated, initialed, and explained, if necessary, and shall not obscure the original entry. An audit trail shall be maintained which will be made available for review by the Sponsor or its representative. Any queries to the data will be addressed by the study center staff in a timely manner.

13.2. *Data Retention*

The investigator will maintain, at the investigative site, in original format all essential study documents and source documentation that support the data collected on study subjects in compliance with ICH/GCP guidelines. Documents must be retained for at least 2 years after the last approval of a marketing application or until at least 2 years have elapsed since the

formal discontinuation of the clinical investigation of the product. These documents will be retained for a longer period of time by agreement with the Sponsor or in compliance with other local regulations. It is BSC's responsibility to inform the investigator when these documents no longer need to be maintained. The investigator will take measures to ensure that these essential documents are not accidentally damaged or destroyed. If for any reason the investigator withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility and BSC must receive written notification of this custodial change.

14. Amendments

If a protocol revision is necessary for reasons including but not limited to, the rights, safety or welfare of the subject, or scientific integrity of the data, an amendment is required. Appropriate approvals (e.g., IRB/EC/FDA/CA) of the revised protocol must be obtained prior to implementation.

15. Deviations

An Investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. An investigator shall notify the sponsor and the reviewing IRB/EC of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency, and those deviations which affect the scientific integrity of the clinical investigation. Such notice shall be given as soon as possible, but no later than 5 working days after the emergency occurred, or per prevailing local requirements, if sooner than 5 working days.

All deviations from the investigational plan, with the reason for the deviation and the date of occurrence, must be documented and reported to the Sponsor. Study centers may also be required to report deviations to their IRB/EC, per local guidelines and government regulations.

Deviations will be reviewed and evaluated on an ongoing basis and, as necessary, appropriate corrective and preventive actions (including notification, center re-training, or discontinuation) will be put into place by the Sponsor.

16. Device/Equipment Accountability

This is a post-market study and therefore no investigational devices are being used. All commercial and institutional policies regarding but not limited to device use, purchase and/or storage will be followed.

17. Compliance

17.1. *Statement of Compliance*

This study will be conducted in accordance with ICH/GCP Guidelines, ethical principles that have their origins in the Declaration of Helsinki, and pertinent individual country laws and regulations. The study shall not begin until the required approval/favorable opinion from the IRB/EC and/or regulatory authority has been obtained, as appropriate. Any additional requirements imposed by the IRB/EC or regulatory authority shall be followed, if appropriate.

17.2. *Investigator Responsibilities*

The Principal Investigator of an investigational center is responsible for ensuring that the study is conducted in accordance with the Clinical Study Agreement, the investigational plan/protocol, ISO 14155, ethical principles that have their origins in the Declaration of Helsinki, any conditions of approval imposed by the reviewing IRB/EC, and prevailing local and/or country laws and/or regulations, whichever affords the greater protection to the subject.

The Principal Investigator's responsibilities include, but are not limited to, the following.

- Prior to beginning the study, sign the Investigator Agreement and Protocol Signature page documenting his/her agreement to conduct the study in accordance with the protocol.
- Provide his/her qualifications and experience to assume responsibility for the proper conduct of the study and that of key members of the center team through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.
- Make no changes in or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency; document and explain any deviation from the approved protocol that occurred during the course of the clinical investigation.
- Create and maintain source documents throughout the clinical study and ensure their availability with direct access during monitoring visits or audits; ensure that all clinical-investigation-related records are retained per requirements.
- Ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.
- Record, report, and assess (seriousness and relationship to the device/procedure) every adverse event and observed device deficiency.
- Report to BSC, per the protocol requirements, all SAEs and device deficiencies that could have led to a SADE.

- Report to the IRB/EC and regulatory authorities any SAEs and device deficiencies that could have led to a SADE, if required by the national regulations or this protocol or by the IRB/EC, and supply BSC with any additional requested information related to the safety reporting of a particular event.
- Allow the sponsor to perform monitoring and auditing activities, and be accessible to the monitor and respond to questions during monitoring visits.
- Allow and support regulatory authorities and the IRB/EC when performing auditing activities.
- Ensure that informed consent is obtained in accordance with this protocol and local IRB/EC requirements.
- Provide adequate medical care to a subject during and after a subject's participation in a clinical study in the case of adverse events, as described in the Informed Consent Form (ICF).
- Inform the subject of the nature and possible cause of any adverse events experienced.
- Inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required.
- Ensure that clinical medical records are clearly marked to indicate that the subject is enrolled in this clinical study.
- Ensure that, if appropriate, subjects enrolled in the clinical investigation are provided with some means of showing their participation in the clinical investigation, together with identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided).
- Inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation.
- Make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from clinical investigation while fully respecting the subject's rights.
- Ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation.
- Ensure that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable.

17.2.1. Delegation of Responsibility

When specific tasks are delegated by an investigator, included but not limited to conducting the informed consent process, the investigator is responsible for providing appropriate training and adequate supervision of those to whom tasks are delegated. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

17.3. *Institutional Review Board/ Ethics Committee*

Prior to gaining Approval-to-Enroll status, the investigational center will provide to the sponsor documentation verifying that their IRB/EC is registered or that registration has been submitted to the appropriate agency, as applicable according to national/regulatory requirements.

A copy of the written IRB/EC and/or competent authority approval of the protocol (or permission to conduct the study) and Informed Consent Form, must be received by the sponsor before recruitment of subjects into the. Prior approval must also be obtained for other materials related to subject recruitment or which will be provided to the subject.

Annual IRB/EC approval and renewals will be obtained throughout the duration of the study as required by local/country or IRB/EC requirements. Copies of the Investigator's reports and the IRB/EC continuance of approval must be provided to the sponsor.

17.4. *Sponsor Responsibilities*

All information and data sent to BSC concerning subjects or their participation in this study will be considered confidential by BSC. Only authorized BSC personnel or a BSC representative will have access to these confidential records. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study. Study data collected during this study may be used by BSC for the purposes of this study, publication, and to support future research and/or other business purposes. All data used in the analysis and reporting of this study will be without identifiable reference to specific subject name.

BSC will keep subjects' health information confidential in accordance with all applicable laws and regulations. BSC may use subjects' health information to conduct this research, as well as for additional purposes, such as overseeing and improving the performance of its device, new medical research and proposals for developing new medical products or procedures, and other business purposes. Information received during the study will not be used to market to subjects; subject names will not be placed on any mailing lists or sold to anyone for marketing purposes.

17.5. *Insurance*

Where required by local/country regulation, proof and type of insurance coverage, by BSC for subjects in the study will be obtained.

18. Monitoring

Monitoring will be performed during the study to assess continued compliance with the protocol and applicable regulations. In addition, the monitor verifies that study records are adequately maintained, that data are reported in a satisfactory manner with respect to timeliness, adequacy, and accuracy, and that the investigator continues to have sufficient staff and facilities to conduct the study safely and effectively. The investigator/institution

guarantees direct access to original source documents by BSC personnel, their designees, and appropriate regulatory authorities.

The study may also be subject to a quality assurance audit by BSC or its designees, as well as inspection by appropriate regulatory authorities. It is important that the investigator and relevant study personnel are available during on-site monitoring visits or audits and that sufficient time is devoted to the process.

19. Potential Risks and Benefits

19.1. *General*

The risks and benefits of performing a suburethral sling procedure in the following subjects should be carefully considered due to additional risks associated with their conditions:

- Women planning future pregnancies
- Overweight women (weight parameters to be determined by the physician)
- Subjects with blood coagulation disorder
- Subjects with a compromised immune system or any other condition that would compromise healing
- Subjects with renal insufficiency or upper urinary tract obstruction

19.2. *Anticipated Adverse Events*

The following anticipated adverse events (AE) have been reported due to suburethral sling placement, but are not limited to:

- Abscess
- Allergic reaction
- Bleeding
- Bruising/Hematoma
- Dehiscence of vaginal incision
- Detrusor Instability
- De Novo Dyspareunia
- Edema/Erythema
- Exposure
- Erosion
- Extrusion

- Fistula
- Hemorrhage
- Incontinence
- Infection
- Inflammation
- Irritation
- Migration of device from desired location
- Neuromuscular Events
- Ongoing pain (pelvic, vaginal, groin/thigh)
- Organ perforation
- Overactive bladder
- Pain
- Re-surgery
- Scarring/Scar contracture
- Urinary Retention
- Urinary Tract Obstruction
- Vessel/Nerve Injury
- Vaginal Discharge
- Sexual Dysfunction

19.2.1. Mesh Exposure and Erosion Event Classification

Assessment of mesh exposure and/or erosion will occur at all follow-up visits post the 2 weeks telephone visit with physical exams performed at 6 weeks, 6, 12, 24, and 36 Months. Identification of mesh exposure and/or erosion will occur by the medical staff member performing the physical exam and will be documented as an adverse event on the Case Report Forms. [redacted]

[redacted]

The classification of these events will be captured through eCRFs.

19.3. *Risks associated with Participation in the Clinical Study*

There are no additional risks with participation in this clinical study outside of the anticipated risks (reference Section 19.2) for stress urinary incontinence as conducted according to standard of care procedures.

19.4. *Risk Minimization Actions*

Additional risks may exist. Risks can be minimized through compliance with this protocol, performing procedures in the appropriate hospital environment, adherence to subject selection criteria, close monitoring of the subject's physiologic status during research procedures and/or follow-ups and by promptly supplying BSC with all pertinent information required by this protocol.

19.5. *Anticipated Benefits*

Theoretical benefits of single-incision or transobturator mid-urethral slings may include reduction in incontinence episodes or resolution of symptoms via a minimally invasive surgical procedure.

[redacted]

20. Informed Consent

Subject participation in this clinical study is voluntary. Informed Consent is required from all subjects or their legally authorized representative. The Investigator is responsible for ensuring that Informed Consent is obtained prior to performing any study-required procedures and/or testing, or data collection.

The obtaining and documentation of Informed Consent must be in accordance with the principles of the Declaration of Helsinki, ISO 14155, any applicable national regulations, and local Ethics Committee and/or Regulatory authority body, as applicable. The ICF must be approved by the center's IRB/EC, or central IRB, if applicable.

Boston Scientific will provide a study-specific template of the ICF to investigators participating in this study. The ICF template may be modified to meet the requirements of the investigative center's IRB/EC. Any modification requires approval from BSC prior to use of the form. The ICF must be in a language understandable to the subject and if needed, BSC will assist the center in obtaining a written consent translation. Translated consent forms must also have IRB/EC approval prior to their use. Privacy language shall be included in the body of the form or as a separate form as applicable.

The process of obtaining Informed Consent shall:

- be conducted by the Principal Investigator or designee authorized to conduct the process,
- include a description of all aspects of the clinical study that are relevant to the subject's decision to participate throughout the clinical study,
- avoid any coercion of or undue influence of subjects to participate,
- not waive or appear to waive subject's legal rights,
- use native language that is non-technical and understandable to the subject or his/her legal representative,
- provide ample time for the subject to consider participation and ask questions if necessary,
- ensure important new information is provided to new and existing subjects throughout the clinical study.

The ICF shall always be signed and personally dated by the subject or legal representative and by the investigator or an authorized designee responsible for conducting the informed consent process. If a legal representative signs, the subject shall be asked to provide informed consent for continued participation as soon as his/her medical condition allows. The original signed ICF will be retained by the center and a copy of the signed and dated document and any other written information must be given to the person signing the form.

Failure to obtain subject consent will be reported by BSC to the applicable regulatory body according to their requirements (e.g., FDA requirement is within 5 working days of learning of such an event). Any violations of the informed consent process must be reported as deviations to the sponsor and local regulatory authorities (e.g. IRB/EC), as appropriate.

If new information becomes available that can significantly affect a subject's future health and medical care, that information shall be provided to the affected subject(s) in written form via a revised ICF or, in some situations, enrolled subjects may be requested to sign and date an addendum to the ICF. In addition to new significant information during the course of a study, other situations may necessitate revision of the ICF, such as if there are amendments to the protocol, a change in Principal Investigator, administrative changes, or following annual review by the IRB/EC. The new version of the ICF must be approved by the IRB/EC. Boston Scientific approval is required if changes to the revised ICF are requested by the center's IRB/EC. The IRB/EC will determine the subject population to be re-consented.

A Screening/Enrollment Log will be maintained to document select information about candidates who fail to meet the general or "other specific" entry criteria.

21. Safety Reporting

21.1. *Definitions and Classification*

Adverse event definitions are provided in Table 21.1-1. Administrative edits were made to combine definitions from ISO 14155-2011 and MEDDEV 2.7/3 12/2010.

Table 21.1-1: Adverse Event Definitions

Term	Definition
Adverse Event (AE) *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3 12/2010*	Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, whether or not related to the investigational medical device. NOTE 1: This includes events related to the investigational medical device or comparator. NOTE 2: This definition includes events related to the procedures involved (any procedure in the clinical investigation plan). NOTE 3: For users or other persons, this definition is restricted to events related to the investigational medical device.
Serious Adverse Event (SAE) *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3 12/2010*	Adverse event that: • Led to death, • Led to serious deterioration in the health of the subject, that either resulted in: o a life-threatening illness or injury, or o a permanent impairment of a body structure or a body function, or o in-subject or prolonged hospitalization of existing hospitalization, or o medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function • Led to fetal distress, fetal death, or a congenital abnormality or birth defect. **NOTE 1**: Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without serious deterioration in health, is not considered a serious adverse event.
Device Deficiency *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3 12/2010*	A device deficiency is any inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. **NOTE 1**: Device deficiencies include malfunctions, misuse or use errors, and inadequate labeling.

Abbreviations: EC=Ethics Committee; IRB=Institutional Review Board

Underlying diseases are not reported as AEs unless there is an increase in severity or frequency during the course of the investigation. Death should not be recorded as an AE, but should only be reflected as an outcome of a specific SAE (see Table 21.1-1 for AE definitions).

Any device related or study procedure related AE experienced by the study subject after informed consent, whether during or subsequent to the procedure, must be recorded in the CRF. Only device and procedure-related AE's are captured in this study.

Refer to Section 19 for the known risks associated with the study device(s).

21.2. *Relationship to Study Device(s)*

The investigator must assess the relationship of the AE to the study device as related or unrelated. See criteria in Table 21.2-1:

Table 21.2-1: Criteria for Assessing Relationship of Study Device to Adverse Event

Classification	Description
Unrelated	The adverse event is determined to be due to a concurrent illness or effect of another device/drug and is not related to the investigational product.
Related	• The adverse event is determined to be potentially related to the investigational product, and an alternative etiology is equally or less likely compared to the potential relationship to investigational product, or • There is a strong relationship to investigational product, or recurs on re-challenge, and another etiology is unlikely, or • There is no other reasonable medical explanation for the event.

21.3. *Relationship to Study Procedure*

The investigator must assess the relationship of the AE to the study procedure as unrelated, possibly related, or probably related. See criteria in Table 21.2-1:

Table 21.3-2: Criteria for Assessing Relationship to Study Procedure

Classification	Description
Unrelated	• No evidence that the timing of the adverse event has a relationship to the procedure performed.
Possibly Related	• The adverse event has a timely relationship to procedure performed. However, a potential alternative etiology may be responsible for the adverse event.
Probably Related	• The adverse event has a timely relationship to the study procedure performed and the causative relationship can be clearly established. No potential alternative etiology is apparent.

21.4. *Investigator Reporting Requirements*

The communication requirements for reporting to BSC are as shown in Table 21.4-1.

Table 21.4-1: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline
Adverse device Effects and Serious Adverse Device Effects. Events assessed for reporting shall include but are not limited to: • Mesh exposure in the vagina • Mesh erosion into the bladder	Complete AE CRF page with all available new and updated information	• Within 2 business days of first becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the study
	If requested by Boston Scientific provide all relevant source documentation (unidentified) for the reported event	• When documentation is available
Adverse Events related to the study procedure for both surgical groups. Events assessed for reporting shall include but are not limited to: • Organ perforation • Bleeding (including hemorrhage and hematoma) • Pelvic pain • Infection • De novo dyspareunia • Urinary retention • Recurrent incontinence • Other urinary problems • Neuromuscular problems • Revision/re-surgery	Complete the AE CRF page, which contains such information as onset date of the AE, treatment provided if any, resolution, assessment of seriousness, and relationship to study device.	• Within 2 business days of first becoming aware of the event or as per local/regional regulations. • • Reporting required through end of subject participation
Device Deficiencies (including but not limited to failures, malfunctions, and product nonconformities) Note: Any Investigational Device Deficiency that might have led to a serious adverse event if a) suitable action had	Complete CRF with all available new and updated information	• Within 1 business day of first becoming aware of the event and as per local/regional regulations • Reporting required through the end of the study

Table 21.4-1: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline
not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event.		

Abbreviations: AE=adverse event; CRF=case report form

[redacted]

21.6. *Reporting to Regulatory Authorities / IRBs / ECs / Investigators*

BSC is responsible for reporting adverse event information to all participating investigators and regulatory authorities, as applicable.

The Principal Investigator is responsible for informing the IRB/EC, and regulatory authorities of an SAE at his/her clinical site as required by local/regional regulations.

[redacted]

[redacted]

23. Suspension or Termination

23.1 Premature Termination of the Study

Boston Scientific Corporation reserves the right to terminate the study at any stage but intends to exercise this right only for valid scientific or administrative reasons and reasons related to protection of subjects. Investigators, associated IRBs/ECs, and regulatory authorities, as applicable, will be notified in writing in the event of study termination.

23.1.1 Criteria for Premature Termination of the Study

Possible reasons for premature study termination include, but are not limited to, the following.

- The occurrence of safety events that present a significant or unreasonable risk to subjects enrolled in the study
- An enrollment rate far below expectation that prejudices the conclusion of the study
- A decision on the part of Boston Scientific to suspend or discontinue development of the device

23.2 Termination of Study Participation by the Investigator or Withdrawal of IRB/ EC Approval

Any investigator, or IRB/ EC in the Solyx Study may discontinue participation in the study or withdrawal approval of the study, respectively, with suitable written notice to Boston Scientific. Investigators, associated IRBs/ECs, and regulatory authorities, as applicable, will be notified in writing in the event of these occurrences.

23.3 Requirements for Documentation and Subject Follow-up

In the event of premature study termination a written statement as to why the premature termination has occurred will be provided to all participating centers by Boston Scientific. The IRB/EC and regulatory authorities, as applicable, will be notified. Detailed information on how enrolled subjects will be managed thereafter will be provided.

In the event an IRB or EC terminates participation in the study, participating investigators, associated IRBs/ECs, and regulatory authorities, as applicable, will be notified in writing. Detailed information on how enrolled subjects will be managed thereafter will be provided by Boston Scientific.

In the event an investigator terminates participation in the study, study responsibility will be transferred to a co-investigator, if possible. In the event there are no opportunities to transfer

investigator responsibility; detailed information on how enrolled subjects will be managed thereafter will be provided by Boston Scientific.

23.4 Criteria for Suspending/Terminating a Study Center

Boston Scientific Corporation reserves the right to stop the inclusion of subjects at a study center at any time after the study initiation visit if no subjects have been enrolled for a period beyond 12 months after center initiation, or if the center has multiple or severe protocol violations/noncompliance without justification and/or fails to follow remedial actions.

In the event of termination of investigator participation, all testing equipment, as applicable, will be returned to BSC unless this action would jeopardize the rights, safety or well-being of the subjects. The IRB/EC and regulatory authorities, as applicable, should be notified. All subjects enrolled in the study at the center will continue to be followed per protocol requirements. The Principal Investigator at the center must make provision for these follow-up visits unless BSC notifies the investigational center otherwise.

[redacted]

[redacted]

[redacted]

[redacted]

26. Abbreviations and Definitions

26.1. *Abbreviations*

Abbreviations are shown in Table 26.1-1.

Table 26.1-1: Abbreviations

Abbreviation/Acronym	Term
Refer to Manual of Operations	

26.2. *Definitions*

Terms are defined in Table 26.2-1.

Table 26.2-1: Definitions

Term	Definition
Refer to Manual of Operations	

Abbreviations are defined in Table 26.1-1.

[redacted]