# STATISTICAL ANALYSIS PLAN

**PRODUCT UNDER INVESTIGATION:**

Spanner® Temporary Prostatic Stent

**TITLE:**

Use of The Spanner® Temporary Prostatic Stent as an Alternative to a Urinary Catheter to Achieve Bladder Drainage in Men Unfit for Other Treatments

**REFERENCE NUMBER:**

CIP Reference Number SRS 1.0

**STUDY SPONSOR**

SRS Medical Systems, Inc.
76 Treble Cove Road, Building 3
North Billerica, MA 01862

**PREPARED BY**

WCCT Global
5630 Cerritos Ave.
Cypress CA 90630

**DATE AND VERSION**

April 1, 2019 (version 2.0)
Based on Rev. D, November 13, 2015 of the protocol, TLFs 1.0, and SRS 2.0 SAP Index 2.0

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# 2. LIST OF ABBREVIATIONS AND DEFINITIONS

| **Abbreviations** | | |
|---|---|---|
| Abbreviation | Abbreviated Term | Definition |
| AE | Adverse Event | Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in patients, users or other persons, whether or not related to the investigational medical device. NOTE 1: This definition includes events related to the investigational medical device or the comparator. NOTE 2: This definition includes events related to the procedures involved. NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices. |
| CSR | Clinical Study Report | Clinical Study Report |
| DSMB | Data Safety and Monitoring Board | An independent data monitoring committee, established by the sponsor, to assess at intervals, the progress of a clinical trial, the safety data and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify or stop a trial. |
| eCRF | Electronic Case Report Form | An electronic document designed to record all of the protocol requested information to be reported to the sponsor on each study patient. eCRFs are "living documents" in the respect that new information on the patient is continually gathered throughout the study. |
| FAS | Full Analysis Set | The Full Analysis Set (FAS) population is a subset of ITT including only those patients in whom the Pipeline™ device was implanted. |
| FDA | Food and Drug Administration | Food and Drug Administration |
| ICF | Informed Consent Form | The written, signed and dated document that provides objective evidence of the process by which a patient voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the trial that are relevant to the patient's decision to participate (21 CFR 50). |
| ICH | International Conference for Harmonization | An Organization whose main purpose is to achieve greater harmonization to ensure that safe, effective, and high quality medicines are developed and registered in the most resource-efficient manner. |
| IDE | Investigational Device Exemption | An approved IDE permits a device that would otherwise be required to comply with a performance standard or would require a premarket approval to be shipped lawfully for the purpose of conducting investigations of that device (21 CFR 812). |
| I/E | Inclusion/Exclusion Criteria | A list of conditions that would include or exclude a patient from enrolling/participating in a clinical study as outlined in the study protocol. |
| IPSS | International Prostate Symptom Score | International Prostate Symptom Score |
| IRB | Institutional Review Board | Any board, committee, or other group formally designated by an institution to review biomedical research involving patients and established, operated and functioning in conformance with 21 CFR 56. |

| **Abbreviations** | | |
|---|---|---|
| Abbreviation | Abbreviated Term | Definition |
| ITT | Intent-to-Treat | The Intention to Treat (ITT) population includes all enrolled patients in whom deployment of the Pipeline™ device was attempted. It is possible that the Pipeline™ device may not reach the target site and the operator would not attempt to deploy it, in the rare event that happens, that patient will not be considered part of the ITT population. |
| MedDRA | Medical Dictionary for Regulatory Activities | Standardized medical terminology developed by ICH to facilitate sharing of regulatory information internationally for medical products used by humans. It is used for registration, documentation and safety monitoring of medical products both before and after a product has been authorized for sale. Products covered by the scope of MedDRA include pharmaceuticals, vaccines and drug-device combination products. |
| PP | Per Protocol | The Per Protocol (PP) population is all enrolled patients that had the Pipeline™ device implanted, and were followed without any major protocol deviations. |
| PVR | | post-void residual |
| SAE | Serious Adverse Event | Adverse event that a) led to death, b) led to serious deterioration in the health of the patient, that either resulted in 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, or 3) in-patient or prolonged hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, c) led to fetal distress, fetal death or a congenital abnormality or birth defect. NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event. |
| SADE | Serious Adverse Device Effect | Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. |
| SAP | Statistical Analysis Plan | Statistical Analysis Plan |
| SD | Standard Deviation | Standard Deviation |
| UADE | Unanticipated Adverse Device Effect | Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity or degree of incidence in the Investigational Plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of patients. |
| ULN | Upper Limit of Normal | Upper limit within a particular range. |
| USADE | Unanticipated Serious Adverse Device Effect | Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report. |

# 3. INTRODUCTION

## 3.1. Purpose of this Document

This document provides a detailed description of the statistical methods and procedures to be implemented during the analysis of protocol SRS 1.0. The methods and procedures are intended to support the generation of a Clinical Study Report (CSR), including detailed descriptions of the populations and methodologies, as well as the post-text tables, analysis summary tables, patient data listings, and descriptive graphics.

This study is a prospective, multicenter, single-arm, open-label trial enrolling approximately 105 patients who are dependent on a urinary catheter. The primary objective is to determine the proportion of patients who achieve adequate bladder drainage over 90 days, defined as a post-void residual (PVR) of ≤150 ml. The pre-specified success criterion for this study is that ⩾50 percent of patients will achieve adequate bladder drainage over 90 days.

The planned analyses identified in this statistical analysis plan (SAP) may be included in regulatory submissions and/or future manuscripts. Exploratory analyses, not identified in this SAP, may be performed to support the clinical development program. Any post-hoc, or unplanned, analyses that are performed but not identified in this SAP will be clearly identified in the CSR. The structure and content of this SAP provides sufficient detail to meet the requirements identified by the FDA and International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): Guidance on Statistical Principles in Clinical Trials.

## 3.2. Supporting Documents

This SAP is intended to be used in conjunction with the following documents:

- The protocol, SRS 1.0
- The list of tables, listings, and figures, SRS SAP Index 2.0
- The templates of tables, listings, and figures, SRS TLF 1.0.

The template document shows all of the data that will be summarized, graphed or listed. For this reason, this document does not enumerate the data variables, but simply refers to the appropriate table, listing, or figure.

# 4. STUDY OBJECTIVES AND ENDPOINTS

## 4.1. Study Objectives

The primary objective of this study is to determine the proportion of patients who achieve adequate bladder drainage over 90 days, defined as a post-void residual (PVR) of ≤150 ml. The pre-specified success criterion for this study is that ≥50 percent of patients will achieve adequate bladder drainage at each of the 4 evaluations over 90 days. The primary objective will be met if

the one-sided lower bound of the 95% confidence limit for the incidence of patients who achieve adequate bladder drainage at each of the 4 evaluations over 90 days is ≥ 50%.

There are 5 secondary objectives, presented below in the order from the protocol.
● To measure the effects of the Spanner stent on bladder drainage, defined by the proportion of patients who achieve a post-void residual of ≤150 ml over 30 days.

● To measure the effects of the Spanner stent on bladder drainage, defined by the proportion of patients who achieve a post-void residual of ≤250 ml over 30 days.

● To measure the effects of the Spanner stent on bladder drainage, defined by the proportion of patients who achieve a post-void residual of ≤250 ml over 90 days.

● To measure the effects of the Spanner stent over time on maximum flow rate (Qmax in ml/sec) as assessed by Uroflow

● To measure the effects of the Spanner stent over time on the International Prostate Symptom Score (IPSS)

The 5 secondary objectives will be summarized and presented descriptively. No formal hypothesis test will be performed for the secondary objectives.

## 4.2. Endpoints

The data from this clinical investigation will based on the investigator / site reported information.

### 4.2.1. Primary Effectiveness Endpoint

PVR levels will be monitored throughout the 90 days of stent use to confirm that the patient is able to successfully empty his bladder. PVR levels are assessed on Visits 1, 2, 3 and 4 while stent is in place using abdominal ultrasound. The hypothesis is that over 90 days of stent use, 50% of the patients will be able to successfully empty their bladder, as defined by PVR of ≤150 ml at all four visits.

Patients where the PVR is >150 ml at 1 or more of the 4 visits will be considered a *treatment failure*. Patients who fail to attend any of the 4 scheduled visits, or withdraw prematurely, will also be treated in primary the analysis as a *treatment failure.* Patients where the PVR is <150 ml at all 4 visits will be considered a *treatment success*.

### 4.2.2. Secondary Effectiveness Endpoints

There are 3 secondary effectiveness endpoints:

**Secondary Effectiveness Endpoint No. 1**
● Patients with a PVR through the first removal visit is ≤150 ml of urine (visit 1 and 2) will be considered as having achieved the first secondary effectiveness endpoint. Patients where the PVR is >150 ml at visit 1 or 2 will be considered as having failed to achieve the first secondary effectiveness endpoint. Patients who fail to attend both scheduled visits, or withdraw prematurely from the study prior to visit 2 will be considered as having failed to achieve the first secondary effectiveness endpoint.

**Secondary Effectiveness Endpoint No. 2**
● Patients with a PVR through the first removal visit is ≤250 ml of urine (visit 1 and 2) will be considered as having achieved the second secondary effectiveness endpoint. Patients where the PVR is >250 ml at visit 1 or 2 will be considered as having failed to achieve the second secondary effectiveness endpoint. Patients who fail to attend both scheduled visits, or withdraw prematurely from the study prior to visit 2 will be considered as having failed to achieve the second secondary effectiveness endpoint.

**Secondary Effectiveness Endpoint No. 3**
● Patients with a PVR through the third removal visit is ≤250 ml of urine (visits 1, 2, 3 and 4) will be considered as having achieved the third secondary effectiveness endpoint. Patients where the PVR is >250 ml at any of the 4 visits will be considered as having failed to achieve the third secondary effectiveness endpoint. Patients who fail to attend all 4 scheduled visits, or withdraw prematurely from the study, will be considered as having failed to achieve the third secondary effectiveness endpoint.

### 4.2.3. Exploratory Effectiveness Endpoints
There are 2 additional exploratory endpoints that will be evaluated in this study:

**Exploratory Effectiveness Endpoint No. 1**
● Change from baseline (visit 1) at visits 2, 3, and 4 in the maximum flow rate (Qmax in ml/sec) as assessed by Uroflow

**Exploratory Effectiveness Endpoint No. 2**
● Change from baseline (visit 2) at visits 3 and 4 in the IPSS Total Symptom Score

Each of the 7 questions that compose the IPSS will be scored on a 0 to 5 scale. The total score can range from 0 to 35. An IPSS Total Symptom Score of 1-7 is considered ***Mild***, 8-19 is considered ***Moderate***, and 20-35 is considered ***Severe***.

# 5. STUDY OVERVIEW

## 5.1. Study Design
This clinical investigation is a prospective, multicenter, single-arm, open-label trial enrolling approximately 105 patients who are dependent on a urinary catheter. Patients will be fitted with a Spanner stent and the stent will be replaced at an interval of approximately 30 days for a total of up to 90 days of use. The Spanner Temporary Prostatic Stent is intended for temporary use (up to 30 days) to maintain urine flow and allow voluntary urination for patients who are not candidates for pharmacologic, minimally invasive or surgical treatment of the prostate. Patients will complete the study upon removal of the Spanner stent after 90 days and one follow-up telephone call post-removal. PVR, uroflow, urinary symptoms, patient satisfaction and the occurrence of adverse events will be collected. Cystoscopy will be performed prior to the initial stent placement and

after the final stent removal to determine any effects of The Spanner on lower urinary tract anatomy.

## 5.2. Study Procedure

Screening is planned to be conducted entirely at Visit 1. Patients who meet the inclusion and exclusion criteria will be enrolled in the study. Device insertion is planned to be conducted at Visit 1. The study will be conducted at three to ten study centers in the US. The study will enroll approximately 105 patients who are dependent on a urinary catheter and meet eligibility criteria. The study will consist of a 90 day treatment period. Patients will be fitted with a Spanner stent and the stent will be replaced at an interval of approximately 30 days (25-35 days permitted) for a total of up to 90 days of use (75-105 days permitted). Patients will complete the study upon removal of the Spanner stent after 90 days and one follow-up telephone call post-removal.

All participants will undergo approximately 90 days of Spanner use, in the form of consecutive Spanner placements each lasting approximately 30 days (25-35 days permitted). During the 90 days, data will be collected with respect to PVR, uroflow, urinary symptoms, patient satisfaction and the occurrence of adverse events. Cystoscopy will be performed prior to the initial stent placement and after the final stent removal to determine any effects of The Spanner on lower urinary tract anatomy.

## 5.3. Sample Size Justification

In order to have an 80% chance of showing that the success proportion in the Spanner group is statistically significantly greater than 50%, assuming that the device can achieve a 65% success rate, with a two-sided type 1 error rate of 5%, a sample size of n=85 completers will be needed for the study. Assuming that a one-sided type 1 error rate of 5% will be adequate, the sample size of 85 completers will provide 88% power. Completers are those subjects whose endpoint is known at 90 days.

Assuming a dropout rate of 20%, the total sample size of n=105 patients will be required for the study. Dropouts are those patients who exit the study prior to completing 90 days without experiencing a PVR failure. The sample size calculation was based on an exact binomial one sample test using PASS 14.0.9 (PASS 14 Power Analysis and Sample Size Software (2015). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass.)

## 5.4. Estimated Duration of Patient Participation

Patients will be enrolled in the trial for a period of up to 125 days, which includes up to 20 days of post-removal follow-up prior to study discharge.

# 6. SCHEDULE OF ASSESSMENTS

Refer to Section 12.1 of the protocol for the schedule of assessments.

# 7. ANALYSIS POPULATIONS

The following populations will be considered for the summarization and analysis of the data from this study:

Intention to Treat Population
The Intention to Treat (ITT) population includes The ITT population will consist of any enrolled patient who underwent an attempted Spanner device implant procedure. This population will be used for all of the analyses unless otherwise stated.

Per Protocol Population
The Per Protocol (PP) population will consist of all patients who are enrolled in the study, have been implanted with a Spanner device, and have completed all study visits with no major protocol deviations while enrolled in the study. A major protocol deviation is defined as any protocol deviation that may affect the primary endpoint. The PP population will only be used as an analysis population if the ITT population produces unexpected results that could have been caused by protocol deviations.

Safety Population
The safety population will consist of all subjects who are enrolled in the study.

# 8. ANALYSIS CONVENTIONS

Specific algorithms are discussed for imputing missing or partially missing dates, if deemed appropriate, under specific data topics. Imputed or derived data will be flagged in the individual patient data listings. Imputed data will not be incorporated into any raw or primary datasets. These data are retained in derived (or analysis) datasets.

Total duration on study will be calculated as the difference between the date of informed consent and the last on-study observation. All calculations defining the duration on study will be performed relative to the date of informed consent and follow the algorithm DURATION = [STUDY COMPLETION OR WITHDRAW DATE – INFORMED CONSENT DATE].

**General Conventions for Summarization**
Summary statistics will consist of the number and percentage of responses or counts at each level for categorical variables (e.g. race). For continuous variables, and the sample size (n), mean, median, standard deviation (SD), minimum, and maximum values will be presented.

All mean and median values will be formatted to one more decimal place than the measured value. Standard deviation values will be formatted to two more decimal places than the measured value. Minimum and maximum values will be presented with the same number of decimal places as the measured value.

The number and percentage of responses will be presented in the form XX (XX.X%).

All probability values will be rounded to 4 decimal places; however, the number of digits to be displayed in the CSR tables will depend on the parameter and result. All probability values that round to 0.0000 will be presented as '<0.0001' and p-values that round to 1.0000 will be presented as '>0.9999'. Probability values < 0.05 will be considered to be statistically significant.

- All summary tables will include the analysis population sample size (i.e., number of patients).

- Relative Study Day 1 is defined as the day the patient underwent the initial study procedure. All study days are determined relative to the day the patient underwent the study procedure.

- Baseline values will be defined as those values recorded immediately prior to the study procedure.

- Change from baseline for ratio data will be calculated as follows:

  ***Change = Post-baseline value / baseline value.***

- Change from baseline for differences will be calculated as follows:

  ***Change = Post-baseline value - baseline value.***

- Missing data may have an impact upon the interpretation of the trial data. The primary presentation of the results will be based on the observed data only. A sensitivity analysis (worst-case) will be performed by imputing the outcome for the primary and secondary endpoints as ***failures*** for the binary outcomes if the patient misses an evaluation visit or if the patient withdraws prematurely prior to attending the required visits. Section 14.11 of the protocol contains a discussion on the use of multiple imputation.

- Date variables will be formatted as DDMMMYYYY for presentation.

- SAS® Version 9.2 or more recent, or a similar statistical package will be the statistical software package used for all data analyses.

- All data from this study will be presented in a listing. All listings will be sorted by patient number and visit date, as applicable.

- Table and listing numbering will follow ICH guidelines for post-text table and listing numbering.

**Handling of Missing or Partial Dates for Adverse Events**

If a portion of the start date of an adverse event is missing, or the entire date is missing, and the missing portion results in the treatment emergent determination being indeterminate, the adverse event will be considered *treatment emergent*.

# 9. PATIENT ACCOUNTING AND STUDY DISPOSITION

A complete accounting of patient participation in the study by analysis population will be presented in Table 9 entitled *Patient Accounting and Disposition* (All Screened Patients). The purpose of this table is to provide an accounting of patients from their entrance into the study through the final visit and to account for the evaluations of patients in the major analyses of efficacy and safety, including reasons for early study termination. The table will display the number of patients that were consented and the number and percentage of patients from the ITT and PP populations that:

- Enrolled (n/%)
- Underwent the study procedure (n/%)
- Evaluated at visit 1 (n/%)
- Evaluated at visit 2 (n/%)
- Evaluated at visit 3 (n/%)
- Evaluated at visit 4 (n/%)
- Follow-up Phone Call (n/%)

Listing 1 entitled *Patient Disposition* supports Table 9. This listing will be sorted by patient number and will include the reason the patient was a screen failure, if the patient was not enrolled.

# 10. PROTOCOL DEVIATIONS AND VIOLATIONS

In accordance with ICH E3, Sponsor-defined eligibility and important post-dosing protocol deviations will be identified and listed separately by patient. Deviation type/code provided by the Sponsor will be used to classify the events as:

- Informed consent
- Randomization error
- Safety
- Efficacy
- Other protocol deviations

A listing and tabulation of protocol deviations will be provided in Listing 2 entitled *Protocol Deviations and Violations*. The listing will be sorted by patient number and date of the protocol violation.

# 11. BASELINE PATIENT DATA

## 11.1. Baseline Demographic Factors

All patients in the Safety Population will be included in summary of demographic information using descriptive statistics as described in Section 8 and the data variables as described in the TLF, Table 11.

## 11.2. Urogenital History

LUTS Symptoms during the prior 6 months will be tabulated using descriptive statistics as described in Section 8 and the data variables as described in the SRS TLF, Tables 12 and 13.

## 11.3. Medical History

Data will be summarized and tabulated using descriptive statistics as described in Section 8 and the data variables as described in the SRS TLF, Table 14.

## 11.4. Medications at Screening

Data will be summarized and tabulated using descriptive statistics as described in Section 8 and the data variables as described in the SRS TLF, Table 15.

## 11.5. Physical Examination and Vital Signs

A physical examination will be performed for all patients at the screening visit. The results will be presented as described in the SRS TLF, Table 16.

## 11.6. Digital Rectal Examination

Each patient will undergo a digital rectal examination at visit 1 screening. Data will be summarized and reported in Table 17 as described in the SRS TLF.

## 11.7. Clinical Laboratory Results

Each patient will have a panel of physiological assays at Screening. Data will be summarized and reported in Table 18 as described in the SRS TLF.

## 11.8. Catheterization Status (Prior to Procedure)

Data will be summarized and tabulated using descriptive statistics as described in Section 8 and the data variables as described in the SRS TLF, Table 19.

## 11.9. Cystoscopy: Bulbar Urethra Distal to External Sphincter

Data will be summarized and tabulated using descriptive statistics as described in Section 8 and the data variables as described in the SRS TLF, Table 20.

## 11.10. Cystoscopy: Verumontanum to Bladder

Data will be summarized and tabulated using descriptive statistics as described in Section 8 and the data variables as described in the SRS TLF, Table 21.

### 11.11. Cystoscopy: Bladder Status

Data will be summarized and tabulated using descriptive statistics as described in Section 8 and the data variables as described in the SRS TLF, Table 22.

## 12. PROCEDURE AND DEVICE ACCOUNTABILITY

### 12.1. Measurements with the Surveyor

Data will be summarized and tabulated using descriptive statistics as described in Section 8 and the data variables as described in the SRS TLF, Table 23.

### 12.2. Spanner Selected

Data will be summarized and tabulated using descriptive statistics as described in Section 8 and the data variables as described in the SRS TLF, Table 24.

### 12.3. Spanner Insertion

Data will be summarized and tabulated using descriptive statistics as described in Section 8 and the data variables as described in the SRS TLF, Table 25.

### 12.4. Spanner Removal

Data will be summarized and tabulated using descriptive statistics as described in Section 8 and the data variables as described in the SRS TLF, Table 26.

### 12.5. Urine Drainage Device Used at Study after Spanner

Data will be summarized and tabulated using descriptive statistics as described in Section 8 and the data variables as described in the SRS TLF, Table 27.

### 12.6. Spanner Accountability

Data will be summarized and tabulated using descriptive statistics as described in Section 8 and the data variables as described in the SRS TLF, Table 28.

### 12.7. Surveyor Accountability

Data will be summarized and tabulated using descriptive statistics as described in Section 8 and the data variables as described in the SRS TLF, Table 29.

## 12.8. Device Deficiencies

Data will be summarized and tabulated using descriptive statistics as described in Section 8 and the data variables as described in the SRS TLF, Table 30.

# 13. EFFICACY

This section will discuss the tabulation and analysis of the study objectives. Detailed descriptions of the statistical procedures that will be used to analyze the study endpoints will be described below.

## 13.1. PVR Summary Statistics

Data will be summarized and tabulated using descriptive statistics as described in Section 8 and the data variables as described in the SRS TLF, Table 31.

## 13.2. Primary Effectiveness Endpoint Analysis

The results of the Primary Effectiveness Endpoint analysis will be presented in the SRS TLF, Table 31.

The primary effectiveness endpoint for this study is the proportion of patients who achieve adequate bladder drainage over 90 days, defined as a post-void residual (PVR) of ≤150 ml. The pre-specified success criterion for this study is that ≥50 percent of patients will achieve adequate bladder drainage at each of the 4 evaluations over 90 days. The primary objective will be met if the one-sided lower bound of the 95% confidence limit for the incidence of patients who achieve adequate bladder drainage at each of the 4 evaluations over 90 days is ≥ 50%. The null and alternative hypotheses are as follows:

$$H_o: \pi \leq 0.5$$

$$H_a: \pi > 0.5$$

$\pi$ is the proportion of patients with maintenance of successful voiding during the Spanner implantation period.

Results based on the ITT population will be presented in Table 32 entitled *Primary Effectiveness Endpoint Analysis* (PVR of ≤150 ml) (ITT population). The table will contain the point estimate and the confidence limit based on patients who met the primary endpoint.

## 13.3. Secondary Effectiveness Endpoints Analyses

The results of the Primary Effectiveness Endpoint analysis will be presented in the SRS TLF, Table 33.

The second effectiveness endpoints for this study are all based on the proportion of patients who achieve adequate bladder drainage at different PVR thresholds.

- PVR of ≤150 ml over 30 days.
- PVR of ≤250 ml over 30 days.
- PVR of ≤250 ml over 90 days.

## 13.4. Analysis of the Exploratory Effectiveness Endpoints

The results of the Exploratory Effectiveness Endpoint analysis will be presented as described in the SRS TLF, Tables 34 through 39. These include summary statistics (as described in Section 8) of the Qmax, IPSS, and QoL results. Both the ITT and PP groups will be described.

# 14. SAFETY

The following sections describe how the safety results (adverse events) will be summarized. All safety results will be presented using the Safety population.

## 14.1. Adverse Events Classification

### 14.1.1. Reporting of Adverse Events

The following information regarding each AE will be obtained: date and time of onset and resolution (duration), severity (defined below), whether it was serious, any required treatment or action taken, outcome, relationship to the investigational device, whether anticipated or unanticipated per protocol definition.

The definitions of seriousness, severity, relationship to device, and outcome are provided in the SRS Protocol.

### 14.1.2. Missing and Partial Adverse Event Dates

The recorded dates for adverse events are important for an accurate tabulation of both events and patients, and required for the following:

1. Defining the start of the event
2. Designation of unique adverse event occurrences recorded intra-patient.

Completely missing or partially missing adverse event dates will be imputed as follows, after due diligence to obtain accurate adverse event information has failed.

If the adverse event start date is completely missing the adverse event will be counted unless it can be determined that the adverse event end date occurred prior to the start of the study procedure. If the adverse event end date can be established as prior to the date of the study procedure, the adverse event will be considered as having occurred prior to the start of the study procedure and will not be counted.

If the adverse event start date is partially missing and the partial date is not sufficient to determine if the event occurred after the start of the study procedure, then the adverse event will be counted unless it can be determined that the adverse event end date occurred prior to the study procedure.

## 14.2. Analysis of Adverse Events

The results of the safety analyses will be presented as described in the SRS TLF, Tables 40 through 44. These include summary statistics (as described in Section 8) of the following safety attributes:

- Overall summary of adverse events
- Adverse events related to the study device or study procedure
- Adverse events related to the study device or study procedure by study visit
- Serious adverse events
- Discontinuations from study participation

# 15. OTHER OUTCOMES

## 15.1. Symptom Interview

The presence or absence of a symptom will be presented at each visit using descriptive statistics as described in Section 8. The results of the analysis will be presented in the SRS TLF, Table 45.

## 15.2. Satisfaction Questionnaire

Patient satisfaction will be assessed on a questionnaire. The data will be summarized and tabulated using descriptive statistics as described in Section 8. The results of the analysis will be presented in the SRS TLF, Table 46.

## 15.3. Clinical Laboratory Results

The data will be summarized and tabulated using descriptive statistics as described in Section 8. The results of the analysis will be presented in the SRS TLF, Table 47.

## 15.4. Telephone Visit

The data will be summarized and tabulated using descriptive statistics as described in Section 8. The results of the analysis will be presented in the SRS TLF, Table 48.

## 15.5. Protocol Deviations – All Enrolled Subjects

The data will be summarized and tabulated using descriptive statistics as described in Section 8. The results of the analysis will be presented in the SRS TLF, Table 49.

## 15.6. Major Protocol Deviations – All Enrolled Subjects

The data will be summarized and tabulated using descriptive statistics as described in Section 8. The results of the analysis will be presented in the SRS TLF, Table 50.

## 15.7. Summary of Objectives and Endpoint Conclusions

The data will be summarized and tabulated using descriptive statistics as described in Section 8. The results of the analysis will be presented in the SRS TLF, Table 51.

# 16. CONTINUING ACCESS PROTOCOL

Most of the tables providing summary data from the Continuing Access Protocol (CAP) are similar to the tables from the pivotal study.

## 16.1. Subject Accounting and Disposition for CAP

The data will be summarized and tabulated using descriptive statistics as described in Section 8. The results of the analysis will be presented in the SRS TLF, Table 52.

## 16.2. CAP PVR Summary Statistics

The data will be summarized and tabulated using descriptive statistics as described in Section 8. The results of the analysis will be presented in the SRS TLF, Table 53.

## 16.3. CAP Primary Effectiveness Endpoint Analysis

The data will be summarized and tabulated using descriptive statistics as described in Section 8. The results of the analysis will be presented in the SRS TLF, Table 54.

## 16.4. CAP Secondary Effectiveness Endpoint Analysis

The data will be summarized and tabulated using descriptive statistics as described in Section 8. The results of the analysis will be presented in the SRS TLF, Table 55.

## 16.5. CAP Exploratory Effectiveness Results Qmax by Visit

The data will be summarized and tabulated using descriptive statistics as described in Section 8. The results of the analysis will be presented in the SRS TLF, Table 56.

## 16.6. CAP Exploratory Effectiveness Results IPSS by Visit

The data will be summarized and tabulated using descriptive statistics as described in Section 8. The results of the analysis will be presented in the SRS TLF, Table 57.

## 16.7. CAP Overall Summary of Adverse Events

The data will be summarized and tabulated using descriptive statistics as described in Section 8. The results of the analysis will be presented in the SRS TLF, Table 58.

## 16.8. CAP Adverse Events Related to the Study Device or Study Procedure

The data will be summarized and tabulated using descriptive statistics as described in Section 8. The results of the analysis will be presented in the SRS TLF, Table 59.

## 16.9. CAP Protocol Deviations

The data will be summarized and tabulated using descriptive statistics as described in Section 8. The results of the analysis will be presented in the SRS TLF, Table 60.