STATISTICAL ANALYSIS PLAN

A Comparison of Direct Aspiration vs. Stent Retriever as a First Approach ("COMPASS")

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Finalized and Reviewed by

Roger B. Johnson, Ph.D.
Director, Biostatistics
and
Eugene C. Poggio, Ph.D.
Chief Biostatistician

Biostatistical Consulting Inc.
91 Hartwell Avenue
Lexington, MA 02421

Signature Page for Analysis Plan

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Finalized and Reviewed by:

Roger B. Johnson, Ph.D. Director of Biostatistics	DocuSigned by: Roger Johnson 1384A3607F5D42E... Signature	12/6/2017 Date
Eugene C. Poggio, Ph.D. Chief Biostatistician	DocuSigned by: Eugene Poggio 7D21ABCAD24B412... Signature	12/6/2017 Date

Biostatistical Consulting Inc.
91 Hartwell Avenue
Lexington, MA 02421

Academic Statistician:

Xiangnan Zhang, M.S.	DocuSigned by: Xiangnan Zhang 3A6F02C2E7224C5... Signature	2017/12/6 Date

Principal Investigators:

J Mocco, M.D., M.S.	DocuSigned by: 7BF270BCA710448... Signature	12/6/2017 Date
Aquilla Turk, D.O.	DocuSigned by: Aquilla Turk D192808268E3481... Signature	12/6/2017 Date
Adnan Siddiqui, M.D., Ph.D.	DocuSigned by: EEC930F984B7495... Signature	12/6/2017 Date

Table of Contents

List of Abbreviations

ADAPT	A Direct Aspiration First Pass Technique
AE	Adverse event
AIS	Acute ischemic stroke
CT	Computed tomography
CTA	Computed tomography angiography
DSMB	Data safety monitoring board
ENT	Emboli to new territory
FU	Follow-up
IAT	Intra-arterial thrombectomy
IRC	Internal review committee
ITT	Intent-to-Treat
IV	Intravenous
LOCF	Last observation carried forward
LTFU	Lost-to-follow-up
LVO	Large vessel occlusion
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
mRS	Modified Rankin scale
NIH	National Institutes of Health
NIHSS	National Institutes of Health Stroke Scale
PP	Per Protocol
SAE	Serious adverse event
SR	Stent retriever
TIA	Transient ischemic attack
TICI	Thrombolysis in cerebral infarction
tPA	Tissue plasminogen activator
UTI	Urinary tract infection

1.0 INTRODUCTION

This document details the analysis plan for the study entitled “A Comparison of Direct Aspiration vs. Stent Retriever as a First Approach ("COMPASS")”. It describes the proposed efficacy and safety analyses.

Acute ischemic stroke remains a potentially devastating condition and is a leading cause of morbidity and mortality affecting an estimated 800,000 people per year in the United States alone and costing an estimated $41 billion in 2007.[1] The most devastating strokes are generally those caused by proximal occlusions in the cervical and cerebral vasculature. The natural history of untreated or unrevascularized large vessel occlusions in acute stroke patients results in mortality rates approaching 30% and only 25% of patients achieving good neurologic outcomes at 90 days.[2, 3] Intravenous (IV) tissue plasminogen activator (tPA) administration is approved for use within 3 hours of symptom onset, with newer evidence suggesting potential benefit out to 4.5 hours.[1, 4-6] However, IV tPA does a poor job of effectively revascularizing large vessel occlusions.[7] Among patients presenting within the approved time window, close to half are ineligible to receive IV tPA due to exclusionary criteria.

Until recently, there had not been a single trial showing efficacy of intra-arterial thrombectomy (IAT) over medical therapy. The MR CLEAN trial showed an absolute difference of 13.5% in rate of functional independence in favor of IAT over medical therapy (32.6% vs 19.1%). MR CLEAN was notable in that it randomized 500 patients in the Netherlands to IV tPA vs. IV tPA and IAT presenting within 6 hours of stroke onset.[8] More robustly, the ESCAPE trial favored IAT over medical therapy by an odds ratio of 2.6 with a significant reduction in mortality (10.4% vs 19.0%). The ESCAPE trial was halted after enrolling 316 patients at 22 centers around the world presenting within 12 hours of stroke onset. ESCAPE was notable in that the trial focused on a select group of high volume centers around the world to do a large number of cases with focus on high technical quality. The trial required advanced imaging to select patients with large vessel occlusion (LVO) and ability to rapidly transition from diagnosis to IAT within 30 minutes.[9] Similarly, the EXTEND IA trial based in Australia was halted after 70 patients were enrolled due to the reported positive results in the MR CLEAN trial. Interim analysis found a marked improvement in ability to achieve functional outcome with IAT (71%) over medical therapy (40%).[10] These trials all utilized advanced imaging to select appropriate patients, and stent retrievers were used for thrombectomy in the majority of cases.

ADAPT is an approach that utilizes the advantages of large bore aspiration catheters that can be easily tracked into the cerebral circulation to directly remove thrombus with a vacuum phenomenon. If this application is not directly effective, then it maintains the thrombus engaged in the catheter tip through suction, and the clot is removed as the catheter is pulled out of the body. In the minority of cases where the application of aspiration is not successful in removing the blockage, then the large aspiration catheter provides a conduit for use of a stent retriever at the location of the thrombus. Initial experience with this approach has shown promising results; however, randomized or direct comparison studies have not been done.[11, 12]

ADAPT, while encompassing the advantages of aspiration with the rescue opportunity of stent retrievers in select cases has not been rigorously tested directly against the approach of stent retrievers as a first line therapy. While inherently suggestive, supportive data on the benefit of aspiration as a first line therapy is limited. The purpose of this study is to demonstrate that patients treated prospectively with the ADAPT approach do not have inferior clinical functional outcomes to those with a stent retriever first line approach.

2.0 STUDY OBJECTIVES

Primary Objective: The primary objective is to show that acute ischemic stroke (AIS) patients, with appropriate image selection, treated with ADAPT approach within 6 hours of symptom onset do not have inferior clinical outcomes to those treated with a first-line stent retriever with 90-day global disability assessed via the modified Rankin Scale score (mRS), analyzed using success criteria as mRS 0 to 2.

Secondary Objective: The secondary objective is to evaluate whether the ADAPT approach is technically superior, clinically superior, or more cost effective than stent retriever as a first line approach in the treatment of AIS.

3.0 STUDY DESIGN

3.1 Overview

This is a prospective, randomized, multicenter, international trial comparing mechanical thrombectomy with the ADAPT approach to stent retrievers as a first line approach (SRFL) in patients presenting with AIS within 6 hours of symptom onset. Any cleared mechanical stent retriever (SR) or aspiration catheter device that is in common use in the operator's region of practice is approved for use.

A total of approximately 270 subjects will be enrolled at up to 20 centers.

The schedule of events for this study is presented in Table 1.

Table 1: Schedule of Events

Activity	Baseline	Randomization/ Procedure	24 hrs Post-Randomization	7 Days Post-Randomization or Discharge	30 d Post-Randomization	90 d Post-Randomization	Neurological Deterioration	Any Add'l FU (if needed)	Study Closure
Evaluation of Criteria	X								
Informed Consent	X								
Randomization		X							
Past Medical History	X								
Clinical Evaluation	X		X	X	X	X	X	X	
Modified Rankin Scale[1]	X		X	X	X	X[2]		X	
NIH Stroke Scale[1]	X		X	X		X[2]	X	X	
Stroke Impact Scale						X			
CT/CTA or MRI/MRA[3]	X		X				X		
Angiogram, TICI Scores		X							
Mechanical Thrombectomy Procedure		X							
Concomitant Medications	X	X	X	X	X	X			
Adverse Event Assessment		X	X	X	X	X	X	X	X

[1]Must be completed by an unbiased healthcare provider.
[2]Must be completed by a BLINDED stroke study team member. If possible, it is preferred for these assessments to be completed by a blinded team member at the other time points also.
[3]CT/CTA or MRI/MRA are required at baseline and 24 hrs post-randomization, and any time there is a neurological deterioration (a change in NIHSS of 4 points or more) or hemorrhage.

3.2 Method of Assigning Subjects to Treatment

Subjects will be randomized in a 1:1 ratio to either the ADAPT approach group or the conventional stent retriever as a first line (SRFL) approach group.

3.3 Blinding

This study is a blinded-assess trial. To avoid bias in the study results, the person performing the primary outcome assessment (as well as NIHSS) at 90 days will be blinded to the subject's treatment assignment and will not have been associated with the care of the subject during the acute treatment phase. All core-lab evaluations will also be blinded.

3.4 Determination of Sample Size

For this study, the sample size was determined by assuming that the true proportions of subjects with mRS outcomes of 0 to 2 at the 90-day follow-up visit (referred to as a success) are similar to the rate of 32.6% (76/233) from recent data from the MR CLEAN trial. The sample size calculations assumed that 33% of ADAPT patients experience success (mRS 0 to 2) and 33% of SRFL patients experience success. Based on a one-sided, normal approximation test for non-inferiority with a non-inferiority margin of 15% and alpha=0.05, 122 patients per treatment group will have 80% power. The sample size was adjusted to 135 patients per treatment group to account for up to 10% attrition. Assuming that the observed success rate for both the ADAPT arm and the SRFL arm is 33% (40/122), the 90% normal approximation confidence interval for the true difference in percentages between treatments is (-9.9%, 9.9%). Sample size was computed using SAS version 9.4.

3.5 Changes to the Protocol-Specified Analyses

According to the protocol, patients who meet the inclusion and exclusion criteria, consent to participate, and who are randomized will be considered enrolled. To clarify, the intent was, and remains, to consider all randomized patients to be enrolled. The intent of the protocol text was to report the sequence of enrollment and not to imply that randomized patients would subsequently be excluded if they were later found to have been incorrectly assessed in regards to inclusion/exclusion criteria.

The protocol defined percent lesion change as follows:

100 x [24 hr Final Infarct Volume - Pretreatment Core Lesion Volume]/24 hr Final Infarct Volume. Instead the denominator will be Pretreatment Core Lesion volume.

In order to utilize a positive non-inferiority margin rather than a negative non-inferiority margin, the null and alternative hypotheses were revised to the equivalent but simpler specification as follows:

$$H_0: \quad p_c - p_t \geq 0.15$$

and

$$H_1: \quad p_c - p_t < 0.15.$$

where p_t and p_c represent the true success proportions for treatment (ADAPT) and control (SRFL), respectively. These hypotheses are entirely equivalent to those in the protocol.

According to the protocol, the null hypothesis was to be tested using a binomial comparison. Instead, this endpoint will be analyzed using a logistic regression model with the following terms in the model: treatment, ASPECTS score at baseline, patient age, sidedness, and any other baseline characteristic for which there is a statistically significant difference between treatments.

Secondary efficacy endpoints/outcomes were listed but not rigidly explained in the protocol. To further clarify we have pre-specified four Secondary Efficacy Endpoints and eight additional Secondary Efficacy Outcomes, as well as Safety Outcomes and Cost Outcome. We also have added 90-day utility weighted mRS, TICI 3 revascularization within 45 minutes, and Stroke Impact scores as Secondary Efficacy Outcomes. These are listed below.

In the protocol, the secondary efficacy endpoints were to be analyzed using a 0.01 significance level based on the use of the Bonferroni method to adjust for multiplicity. Instead, the secondary efficacy endpoints will be analyzed using Holm's stepwise testing procedure to take the multiplicity into account. [13]

4.0 ENDPOINTS AND OUTCOMES

4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is mRS success, defined as a mRS score of 0 to 2 at the 90-day follow-up visit.

4.2 Secondary Efficacy Endpoints

- Time from groin puncture to thrombolysis in cerebral infarction (TICI) 2b or better revascularization
- 90-day global disability assessed via the overall distribution of mRS
- TICI 2c or greater revascularization within 45 minutes of access.
- TICI 3 revascularization within 45 minutes of access.

4.3 Secondary Efficacy Outcomes

- TICI 2b or greater revascularization within 45 minutes of access.
- Occurrence of emboli to a new territory.
- Presence of vasospasm involving the accessed vascular tree
- 90-day global disability assessed via the overall distribution of the utility weighted mRS
- Reduction in stroke severity (NIHSS) at 24 hours post treatment
- Reduction in stroke severity (NIHSS) at 7 days post treatment or discharge (whichever occurs first)
- Stroke Impact Score
- First pass TICI 2b or greater efficacy

4.4 Safety Outcomes

The primary safety outcomes to be assessed at completion of the trial are:

- Symptomatic intracranial hemorrhage at 24 hours post-randomization

- Asymptomatic intracranial hemorrhage at 24 hours post-randomization
- Intracranial hemorrhage within 90 days of randomization
- All intracranial hemorrhage with distinction of PH2 hemorrhage [neurological deterioration (NIHSS worsening 4 or more)] within 36 hours of randomization
- Clinically significant complications (pneumonia, sepsis, UTI, etc.) at time of discharge or 7 days post randomization (whichever comes first)
- Mortality rates at 30 days post-randomization
- Mortality rates at 90 days post-randomization
- Treatment-related serious adverse events (SAEs) up to 48 hours post-randomization
- Procedure-related SAEs

4.5 Cost Outcome

- Device related cost for procedure

5.0 STATISTICAL CONSIDERATIONS

5.1 General Methodology

Data collected in this study will be documented using summary tables. Continuous variables will be summarized using descriptive statistics, specifically the mean, standard deviation, median, minimum, and maximum. For categorical variables, counts and percentages will be provided. All statistical tests will be performed at the 0.05 significance level, unless noted otherwise. For purposes of analysis, nominal visits will be used without regard for visit windows. The statistical analysis of the data obtained from this study will be performed using SAS® version 9.4 or later.

5.2 Adjustments for Covariates

The primary efficacy endpoint will be analyzed using a logistic regression model to test for non-inferiority of ADAPT to SRFL with adjustment for the following baseline covariates: ASPECTS score, patient age, sidedness, and any other baseline characteristic for which there is a statistically significant difference (two-sided p-value < 0.05) between treatments.

The following secondary efficacy endpoints will be analyzed using a logistic regression model to test for a difference between treatments with adjustment for clot location: TICI 2b or greater revascularization within 45 minutes of access, TICI 2c or greater revascularization within 45 minutes of access, and TICI 3 revascularization within 45 minutes of access.

5.3 Handling of Dropouts and Missing Data

Under the Intent-to-Treat (ITT) principle, all patients who are randomized are to be included in the analysis. Therefore, missing data, especially in the outcome measures, can be problematic. Every effort is to be made to keep all missing data, particularly the Day 90 outcomes, to a minimum. Despite the clinical sites' best efforts, some missing data may be inevitable, mainly due to lost-to-follow-up (LTFU). The number and proportion of subjects eligible for and compliant with each follow-up examination will be presented. Subjects who withdraw from the study will be tabulated along with the reasons for withdrawal. For the primary efficacy endpoint, subjects deceased during study follow-up will be scored as mRS 6, as per the standard scoring for mRS. For subjects with missing data, the primary efficacy endpoint will be imputed using the Last-Observation-Carried Forward (LOCF) method, i.e., using the mRS value as of the last available follow-up visit or discharge (whichever is later). A sensitivity analysis will be performed in which subjects with missing data for the primary efficacy endpoint will be scored as mRS 6, i.e., a failure. A second sensitivity analysis will be performed in which subjects with missing data for the primary efficacy endpoint will be excluded.

For the primary analyses of the secondary efficacy endpoints, subjects with missing data for the endpoint will be excluded from the analysis. A sensitivity analysis will be performed for the following secondary efficacy endpoints: TICI 2c or greater revascularization within 45 minutes of access and TICI 3 revascularization within 45 minutes of access. In this sensitivity analysis, subjects with missing values will be classified as failures.

5.4 Interim Analyses and Data Monitoring

No formal interim analyses will be conducted.

The Data Safety Monitoring Board (DSMB) will receive periodic safety reports of all adverse events (AEs) and SAEs. In addition, the treatment-related SAEs occurring within 48 hours of randomization will be monitored as a safety outcome along with the following:

- Symptomatic intracranial hemorrhage within 24 hours of randomization
- Asymptomatic intracranial hemorrhage within 24 hours of randomization
- Mortality rates at 30 days post-randomization
- Mortality rates at 90 days post-randomization
- Treatment-related SAEs during the study
- All SAEs during the study
- Major non- intracranial hemorrhage bleeding complications during hospitalization
- Recurrent stroke within 90 days of randomization

5.5 Multicenter Study

This is a multicenter study. It is planned to enroll approximately 270 subjects at up to 20 clinical study sites.

5.6 Multiple Comparisons / Multiplicity

Formal hypothesis tests will be performed for the secondary efficacy endpoints only if the null hypothesis is rejected for the primary efficacy endpoint, and the analysis of the secondary efficacy endpoints will be performed with adjustment for multiple comparisons using Holm's stepwise testing procedure. No other adjustments for multiple comparisons/multiplicity will be made.

5.7 Examination of Subgroups

No subgroup analyses are planned.

5.8 Definition of Baseline Measurements

For assessments scheduled to be performed at the baseline visit, but not the randomization visit, the baseline value is defined as the value at the baseline visit. For assessments scheduled to be performed at the randomization visit, but not at the baseline visit, the baseline value is defined as the value at the randomization visit.

6.0 ANALYSIS POPULATIONS

6.1 Intent-to-Treat (ITT)

The ITT population will include all randomized subjects. The ITT population will be the primary analysis population for the efficacy endpoints, the cost outcome, and the safety outcomes, and subjects will be analyzed according to the treatment group to which they were assigned at randomization.

6.2 Per Protocol (PP)

The Per Protocol (PP) population will include all randomized subjects who do not have the following protocol violations or deviations:

a. Eligibility violation
b. Treatment crossover, defined as receiving, as initial treatment, the study treatment to which the subject was not randomized
c. Missing 90 day primary outcome (not including missing due to death prior to the 90 days)

The PP population will be used for a secondary analysis of the efficacy endpoints, and subjects will be analyzed according to the treatment group to which they were assigned at randomization.

7.0 SUBJECT DISPOSITION

Patients who are randomized will be considered enrolled. All subjects who are enrolled will be accounted for. The frequency and percentage of subjects eligible for and compliant with each follow-up examination will be presented.

The number and percentage of randomized subjects in the ITT and Per Protocol populations will be presented for each treatment group. The numbers and percentages of randomized subjects who complete the study and who withdraw from the study early, together with the reason for withdrawal, will be presented by treatment group.

The reason(s) for exclusion from the PP Population will be summarized using counts and percentage for randomized subjects.

8.0 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics, including medical history and clinical evaluation, will be summarized using descriptive statistics for continuous variables and frequencies and percentages for categorical variables. Fisher's Exact Test will be used to test for a difference in proportions between treatments for dichotomous variables. The Cochran-Mantel-Haenszel row mean scores test will be used to test for a difference in means between treatments for ordinal categorical variables. The two-sample t-test will be used to test for a difference in means for continuous variables. The variables to be summarized are as follows:

- Age
- Sex
- Medical History
- Sidedness
- Pre-morbid Modified Rankin Score (mRS)
- Baseline National Institutes of Health Stroke Scale (NIHSS)
- Systolic Blood Pressure
- Baseline ASPECTS Score
- Site of Occlusion
- Directly admitted to a comprehensive stroke center
- IV tPA pre-procedure
- General Anesthesia
- Onset to main hospital arrival time
- Onset to groin puncture time
- Onset to qualifying imaging time
- Qualifying imaging to randomization time
- Randomization to groin puncture time

9.0 PROCEDURE

Procedural details will be summarized by treatment group using descriptive statistics for continuous variables and frequencies and percentages for categorical variables. For categorical variables, the odds ratio (ADAPT vs. SR) and corresponding 95% confidence interval will be presented, together with the p-value from a two-sided chi-square test for a difference in true percentages between treatments. Continuous variables will be analyzed using a two-sided, two-sample t-test to test for a difference in means between treatments.

10.0 EFFICACY ANALYSES

10.1 Primary Efficacy Endpoint

The primary effectiveness endpoint is mRS success, defined as a mRS score of 0 to 2 at the 90-day follow-up visit. The number and proportion of patients in each treatment group who are a success will be calculated and the 90% confidence interval for the difference in proportions between treatment groups will be presented. The null and alternative hypotheses for this endpoint are as follows:

H_0: $p_c - p_t \geq 0.15$

and

H_1: $p_c - p_t < 0.15$

where p_t and p_c represent the true success proportions for treatment (ADAPT) and control (SRFL), respectively. This endpoint will be analyzed using a logistic regression model with the following terms in the model: treatment, ASPECTS score at baseline, patient age, sidedness, and any other baseline characteristic for which there is a statistically significant difference between treatments. The p-value for the test of the null hypothesis will be obtained based on a statistic for the difference (control - treatment) in least squares means (actually proportions rather than means) for each treatment minus the non-inferiority margin of 0.15 all divided by the standard errors of the difference in the least squares means and assuming an approximate normal distribution. This test is essentially equivalent to evaluating whether the lower bound of the 90% confidence interval based on the normal approximation for the true difference in least squares means between treatments is less than 0.15.

Subjects deceased during study follow-up will be scored as mRS 6, as per the standard scoring for mRS. For subjects missing data for the primary efficacy endpoint, missing values will be imputed using the Last-Observation-Carried Forward (LOCF) method, i.e., using the mRS value as of the last available follow-up visit or discharge (whichever is later). A sensitivity analysis will be performed for the ITT Population in which subjects with missing data for the primary efficacy endpoint will be scored as mRS 6, i.e., a failure. A second sensitivity analysis will be performed in which subjects with missing data for the primary efficacy endpoint will be excluded.

10.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are presented in Section 4.2. Time from groin puncture to thrombolysis in cerebral infarction (TICI) 2b or better revascularization will be analyzed using the Kaplan-Meier method, and the log-rank test will be used to test for a difference between treatments. 90-day global disability assessed via the overall distribution of mRS, will be summarized using descriptive statistics, and the Cochran-Mantel-Haenszel row mean scores test will be used to test for a difference in means between treatments. TICI 2c or greater revascularization within 45 minutes of access and TICI 3 revascularization within 45 minutes of access will be summarized using frequencies and percentages, and logistic regression with terms for treatment and location of clot will be used to test for a difference in proportions between treatments. For these two endpoints, the odds ratio (ADAPT vs. SRFL) and corresponding 95% confidence interval will be presented. A sensitivity analysis will be performed for the ITT Population for these same two endpoints in which subjects with missing data will be classified as a failure. For the primary analyses of the secondary efficacy endpoints, subjects with missing data for the endpoint will be excluded from the analysis.

Formal hypothesis tests will be performed for the secondary efficacy endpoints only if the null hypothesis is rejected for the primary efficacy endpoint.

Holm's stepwise testing procedure will be used to adjust the significance levels of the tests in the analysis of the secondary efficacy endpoints in order to take multiplicity into account. Holm's procedure is conducted as follows. The ordered p-values $p_{(1)}$, $p_{(2)}$, $p_{(3)}$, and $p_{(4)}$ will be obtained, where the ordering is from least to greatest. The testing procedure begins with the null hypothesis associated with the most significant p-value, i.e., with $H_{(1)}$. This hypothesis is rejected if $p_{(1)} \leq 0.05/4$. If $H_{(1)}$ is not rejected, stop the hypothesis testing. Otherwise, proceed to test $H_{(2)}$, which will be rejected if $p_{(2)} \leq 0.05/3$. If $H_{(2)}$ is not rejected, stop the hypothesis testing. Otherwise, proceed to test $H_{(3)}$, which will be rejected if $p_{(3)} \leq 0.05/2$. If $H_{(3)}$ is not rejected, stop the hypothesis testing. Otherwise, proceed to test $H_{(4)}$, which will be rejected if $p_{(4)} \leq 0.05/1$. If the null hypothesis is rejected for a given secondary efficacy endpoint, p-values for subsequent endpoints will be presented for descriptive purposes only.

10.3 Secondary Efficacy Outcomes

The secondary efficacy outcomes are presented in Section 4.3. TICI 2b or greater revascularization within 45 minutes of access, occurrence of emboli to a new territory, presence of vasospasm involving the accessed vascular tree, and first pass TICI 2b or greater efficacy will be summarized using frequencies and percentages, and logistic regression with terms for treatment and location of clot will be used to test for a difference in proportions between treatments. The odds ratio (ADAPT vs. SRFL) and corresponding 95% confidence interval will be presented. The other secondary efficacy outcomes will be summarized using descriptive statistics and will be analyzed using a two-sided, two-sample t-test to test for a difference in means between treatments.

11.0 SAFETY ANALYSES

Primary safety outcomes are listed in Section 4.4. Each of these outcomes will be summarized by treatment using frequencies and percentages, together with the odds ratio (ADAPT vs. SRFL) and corresponding 95% confidence interval.

12.0 COST ANALYSIS

The analysis of device related cost for procedure will be summarized using descriptive statistics and will be analyzed using a two-sided, two-sample t-test ($p<0.05$) to test for a difference in means between cohorts. These data will take time to acquire and analyze and will be presented in a secondary analysis and publication.

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