



Statistical Analysis Plan

**Chronic Total Occlusion Percutaneous Coronary Intervention
CTO-PCI Study**

Document ID: ST-3041

Revision: C 17 Aug 2020

Signatures

Signature:

Date:

Clinical Director
Ricardo De Medeiros, Teleflex Incorporated

Signature:

Date:

Clinical Study Lead
Joan Hazen, BRIGHT Research Partners

Signature:

Date:

Statistician
Scott Brown, PhD, BRIGHT Research Partners

TABLE OF CONTENTS

1. INTRODUCTION	4
2. ABBREVIATIONS AND DEFINITIONS	4
3. STUDY DESIGN.....	5
4. RANDOMIZATION AND BLINDING	5
5. ANALYSIS POPULATION	5
6. OBJECTIVE	5
7. ENDPOINTS	6
8. GENERAL STATISTICAL CONSIDERATIONS	6
9. GENERAL STATISTICAL SUMMARIES.....	7
10. ANALYSIS OF STUDY ENDPOINTS	8
11. DETERMINATION OF SAMPLE SIZE	9
12. ADDITIONAL ANALYSES	9
13. CHANGES IN PLANNED ANALYSES	9
14. REVISION HISTORY.....	9

1. Introduction

The purpose of this statistical analysis plan (SAP) is to outline the data handling methods and planned analyses to be used for the Teleflex CTO-PCI Study.

2. Abbreviations and Definitions

The abbreviations and definitions described below encompassed terminology utilized in this SAP and/or the corresponding CTO-PCI Clinical Study Protocol.

ACE	Angiotensin converting enzyme
ACT	Activated clotting time
ADE	Adverse device effect
AE	Adverse event
ALT	Alanine aminotransferase
ARB	Angiotensin receptor block
AST	Aspartate aminotransferase
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CEC	Clinical events committee
CFR	Code of federal regulations (U.S.)
CHF	Congestive heart failure
CK	Creatine kinase
CK-MB	Creatine kinase with M (muscle) and B (brain) subunits
CRF	Case report form
(e)CRF	(electronic) case report form
CRO	Contract Research Organization
CTO	Chronic total occlusion
CV	Curriculum vitae
EDC	Electronic data capture
FAS	Full analysis set
FDA	Food and Drug Administration (U.S.)
GCP	Good clinical practice
GUSTO	Global Use of Strategies to Open Occluded Coronary Arteries
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed consent form
ICH	International Conference on Harmonization
IFU	Instructions for use
IRB	Institutional review board
ISO	International Organization for Standardization

MACE	Major cardiac adverse event
MDR	Medical Device Reporting (to FDA)
MI	Myocardial infarction
NYHA	New York Heart Association
O.D.	Outer diameter
PCI	Percutaneous coronary intervention
PI	Principal investigator
PTCA	Percutaneous transluminal coronary angioplasty
PTFE	Polytetrafluoroethylene
SAE	Serious adverse event
SAP	Statistical analysis plan
TIMI	Thrombolysis in myocardial infarction
UADE	Unanticipated (serious) adverse device effect
ULN	Upper limit of normal
URL	Upper reference limit

3. Study Design

The study is a prospective, multicenter, single-arm, intent-to-treat, literature-controlled clinical study.

4. Randomization and Blinding

The study is non-randomized and open-label.

5. Analysis Population

Analyses will be conducted under the principles of intent-to-treat, using the full analysis set (FAS) as defined in ICH E9 (Statistical Principles for Clinical Trials). Primary analyses will include all available data on all enrolled subjects.

6. Objective

The objective of this study is to evaluate angiographic confirmation of placement of any guidewire beyond the CTO, in the true vessel lumen, in patients undergoing CTO percutaneous coronary intervention (PCI) in which at least one Teleflex guidewire and at least one Turnpike catheter are used. The data captured in this study will be used to support FDA 510(k) clearance for a CTO indication.

7. ENDPOINTS

7.1. Primary Endpoint

The primary endpoint is defined as procedure success through discharge or 24 hours post-procedure, whichever comes first.

- Procedure success is defined as angiographic visualization of any guidewire in a position either distal or proximal to the occlusion depending on the route of access and the absence of in-hospital major adverse cardiac events (MACE).
 - In accordance with the study objective (Section 6), the definition of procedure success is to be interpreted as requiring presence of the guidewire in the *true vessel lumen*.
- MACE is defined as any serious adverse experience that includes cardiac death, target lesion revascularization, or post-procedural MI (Q-wave or non-Q-wave, with CK-MB > 3 URL).

7.2. Secondary Endpoints

- Frequency of successful recanalization (defined as angiographic confirmation of crossing the chronic total occlusion and restoring blood flow to the affected area).
- Frequency of MACE through discharge or 24 hours post-procedure, whichever comes first (in-hospital), and at 30 days post-procedure. The components of MACE will also be reported separately.
- Frequency of clinically significant perforation (defined as any perforation resulting in hemodynamic instability and/or requiring intervention including pericardiocentesis, embolization, prolonged balloon occlusion, stent graft, or comparable therapy).
- Procedural success according to crossing technique.
- Technical success.

8. General Statistical Considerations

The following general comments apply to all statistical analyses and data presentations.

8.1. Descriptive Statistics

Continuous data will be summarized using descriptive statistics: n, mean, standard deviation, standard error, median, and range or interquartile range. Discrete variables will be summarized using frequency counts and percentages. For ordinal-scaled variables, a combination of the following may be employed as appropriate: frequency and percentage of observations within a category and means and standard deviations of the scores of the categories.

8.2. Significance level

Unless otherwise specified, statistical analyses will be performed using one-sided hypothesis tests at an overall alpha level of 0.05.

8.3. Duration Variables

Study Day 0 is the day of study device deployment (index procedure). Study day will appear in the listings where applicable and is calculated relative to day 0 using the general formula:

$$\text{Study Day} = (\text{Date of Event} - \text{Date of Study Device Deployment})$$

Duration variables will be calculated using the general formula:

$$[(\text{end date} - \text{start date})]$$

8.4. Missing Data

All available data in the full analysis set will be used to evaluate study outcomes. Methods for replacing missing data such as last value carried forward or multiple imputation will not be routinely used.

8.5. Software

All statistical analyses will be performed using Statistical Analysis System (SAS) for Windows (version 9.4 or higher, SAS Institute Inc. Cary, NC) or R (version 3.2 or higher, R Foundation for Statistical Computing, Vienna, Austria).

9. General Statistical Summaries

9.1. Subject Disposition

Subject accountability and study discontinuation will be summarized. Subject accountability at each visit will be summarized as the number of subjects with complete visits, missed visits, or study discontinuations prior to the visit. All subjects who do not complete the study will be tabulated by reason for discontinuation.

9.2. Demographic and Baseline Characteristics

Demographic and baseline characteristics, including but not limited to age, gender and race, will be summarized.

9.3. Medical History

Medical history will be summarized, including any previous catheterizations, vascular procedures/surgery, and concomitant diseases.

9.4. Adverse Events

An overall summary of adverse events will be presented. The summary will include the number and percentage of subjects who report at least one adverse event and the total number of adverse events. Complete subject listings of all adverse events will be provided.

All adverse events will be arbitrated by the Clinical Events Committee (CEC). The CEC, which is made up of at least two interventional cardiologists who are not investigators in the study, will adjudicate and classify adverse events for seriousness and device and/or procedure relationship.

10. Analysis of Study Endpoints

10.1. Primary Endpoint

The primary endpoint is procedure success through discharge or 24 hours post-procedure, whichever comes first. This endpoint will be assessed for each enrolled subject and presented as a proportion of successes with corresponding confidence limits calculated via the exact binomial method. Note that enrollment occurs when an investigational guidewire has entered the guide catheter.

Results will then be compared to a performance goal derived from the literature on comparable products in the intended study population. Formally, the hypotheses to be tested are as follows:

$$H_0: \mu \leq PG$$

$$H_A: \mu > PG,$$

where μ is the proportion of successes and PG is the performance goal. The hypotheses will be tested at a one-sided alpha level of 0.05 and study success will be declared if the performance goal is met (i.e., if the null hypothesis above is rejected in favor of the alternative hypothesis).

Specific references and resulting analysis for the PG are as follows:

Study	Procedural Success % (n/N)	95% confidence interval
Olivari (2003)	73.3% (286/390)	(68.6%, 77.7%)
Prasad (2007)	69.7% (879/1262)	(67.0%, 72.2%)
Valenti (2008)	70.8% (344/486)	(66.5%, 74.8%)
Kandzari (2015)	79.0% (109/138)	(71.2%, 85.5%)
Kandzari (2018)	73.0% (119/163)	(66.2%, 79.8%)
Meta-analyzed rate	73.2%	

The meta-analyzed rate is derived from study-level pooling incorporating the five studies, with a resulting success rate of 73.2%. Incorporating a 10% statistical delta for hypothesis testing purposes, the performance goal for the primary endpoint is therefore PG = 63.2%.

10.2. Secondary Endpoints

Secondary endpoints will be summarized and tabulated without formal hypothesis testing according to the general principles above.

11. Determination of Sample Size

The postulated success rate for the primary endpoint is estimated to be 73.2%, based on the literature references cited above; the performance goal of 63.2% is as previously defined. Given a one-sided test at 0.05 alpha and desired power of 80%, the required evaluable sample size is 135. A study sample size of 150 total subjects therefore provides adequate powering for hypothesis testing as described above.

12. Additional Analyses

12.1. Subgroup Analyses

No subgroups of interest are prospectively defined for analysis.

12.2. Interim Analysis

No formal interim analysis for the purpose of early stopping is planned, and no formal statistical rule for early termination of this study for insufficient effectiveness of the study devices is defined. The Sponsor reserves the right to terminate or suspend the study for valid scientific or business reasons, or reasons related to the protection of subjects (e.g., the discovery of an unexpected, significant, or unacceptable risk to subjects).

12.3. Pooling of Data

As this investigation is a multi-center study, poolability of the primary endpoint will be assessed using Pearson's chi-square test; for this purpose, only sites enrolling at least five (5) subjects will be included for statistical testing to avoid sparse cells in the analysis. A resulting p-value less than 0.10 will be cause for investigation of potential causes of heterogeneity across clinical sites.

13. Changes in Planned Analyses

Any deviations or changes from this SAP deemed necessary due to violation of critical underlying statistical assumptions, data characteristics, or missing data will be clearly described with justification and rationale.

14. Revision History

Revision	BRIGHT DCO#	Effective Date	Revision Description
1.0	2019-05-003	10 May 2019	Initial Release
A	NA – Document now controlled via Sponsor's Agile document control system	30 Jul 2019	Revised section 9.1 and 11.3 to align with FDA recommendations provided at time of IDE approval. Cover page and page header revision convention corrected from numerical to alphabetical. Document will now be controlled by Sponsor (via Agile system) vs. CRO document control.

Revision	BRIGHT DCO#	Effective Date	Revision Description
B	NA – Document now controlled via Sponsor's Agile document control system	11 Feb 2020	Updated a secondary objective and abbreviations related to changes made in the new protocol rev C.
C	NA – Document now controlled via Sponsor's Agile document control system	17 Aug 2020	Clarified the heading in section 6 to match the protocol and also clarified the primary endpoint (and procedure success definition) requiring presence of the guidewire in the true vessel lumen (as referenced in the study objective). This SAP is being clarified in lieu of an update to the protocol.