Clinical Study Protocol

Chronic Total Occlusion Percutaneous Coronary Intervention
CTO-PCI Study

Study Number: ST-2955

Revision: C, 04-Feb-2020

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Principal Investigator Signature

I have read the clinical study protocol and agree to adhere to the requirements of this protocol in accordance with the ICH guidelines for good clinical practices, ISO 14155, and applicable FDA regulations.

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Teleflex®	**CLINICAL STUDY PROTOCOL SYNOPSIS** **CTO-PCI STUDY** **Teleflex Study Number: ST-2955**
Study Title	Chronic Total Occlusion Percutaneous Coronary Intervention CTO-PCI Study
Identifying Regulatory Numbers	FDA IDE number – G190013 Clinicaltrials.gov – *NCT03988166*
Study Objective	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 U.S. Food and Drug Administration (FDA) 510(k) clearance for CTO indications.
Device Description	Study devices include the GuideLiner® V3 catheter, TrapLiner® catheter, Turnpike® catheter, and a series of five coronary guidewires (Spectre™ guidewire, R350™ guidewire, Raider™ guidewire, Warrior™ guidewire, and Bandit™ guidewire). All study devices are currently 510(k) cleared for non-CTO indications.
Device Indications	• GuideLiner catheters are intended to be used in conjunction with guide catheters to access discrete regions of the coronary and/or peripheral vasculature, to facilitate placement of interventional devices, and to assist in crossing de novo chronic total occlusions (CTO). • The TrapLiner catheter is intended for use in conjunction with guide catheters to access discrete regions of the coronary and/or peripheral vasculature, to facilitate placement of interventional devices, to facilitate the exchange of an interventional device while maintaining the position of a guidewire within the vasculature, and to assist in crossing de novo chronic total occlusions (CTO). • The Turnpike catheters are intended to be used to access discrete regions of the coronary and/or peripheral vasculature. They may be used to facilitate placement and exchange of guidewires, to subselectively infuse/deliver diagnostic and therapeutic agents, and to assist in crossing de novo coronary chronic total occlusions (CTO). • The Teleflex guidewires are intended for use in percutaneous procedures to introduce and position catheters and other interventional devices within the coronary and peripheral vasculature, including use in crossing or assisting in crossing de novo coronary chronic total occlusions (CTO).
Study Design	A prospective, multicenter, single-arm, intent-to-treat, literature-controlled clinical study.

Number of Sites & Subjects	The study will be conducted in up to 15 investigational sites in the U.S. This study will enroll up to 150 patients to provide adequate powering for hypothesis testing and an evaluable sample size of at least 135 patients.
Study Population	The population for this study is subjects with signs and/or symptoms considered typical of ischemic heart disease attributed to a *de novo* CTO in a native coronary artery who are suitable candidates for a percutaneous revascularization.
Primary Endpoint	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). • MACE 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 ULN).
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.
Study Eligibility Criteria	Subjects must meet all of the following inclusion criteria: *General inclusion criteria* 1. At least 18 years of age at the time of consent 2. Experiencing clinical symptoms considered suggestive of ischemic heart disease (e.g., chest pain or discomfort, heart failure) or has evidence of myocardial ischemia (e.g., abnormal functional study) attributed to the CTO target vessel and is scheduled for clinically indicated percutaneous revascularization 3. Subject is eligible and consents to undergo PCI procedure 4. Acceptable candidate for percutaneous transluminal coronary angioplasty (PTCA), stenting, and emergency CABG 5. Willing and able to sign a study Informed Consent Form (ICF) approved by a local or central Institutional Review Board (IRB) 6. Female subjects of childbearing potential must have a negative pregnancy test per standard of care for PCI and be practicing contraception

	Angiographic inclusion criteria 7. A minimum of one de novo lesion with at least one target segment in a native coronary vessel meeting the definition of CTO (any non-acute total coronary occlusion fulfilling the angiographic characteristics consistent with high-grade native coronary stenosis (Thrombolysis in Myocardial Infarction (TIMI) score of 0 or 1) and estimated to be in duration of ≥ 3 months by clinical history and/or comparison with antecedent angiogram or electrocardiogram) Subjects must not meet any of the following exclusion criteria: *General exclusion criteria* 1. History of allergy to iodinated contrast that cannot be effectively managed medically 2. Evidence of acute myocardial infarction (MI) within 72 hours prior to the intended treatment defined as CK-MB greater than 3 times the upper limit of normal (ULN) 3. Previous coronary interventional procedure of any kind within 30 days prior to the procedure 4. Any contraindication to cardiac catheterization or to any of the standard concomitant therapies used during routine cardiac catheterization and PCI (e.g., aspirin, clopidogrel, unfractionated heparin) 5. Target lesion requires treatment with another device, after successful crossing with a study device, other than PTCA devices prior to stent placement 6. Atherectomy procedure is planned for the target lesion 7. Known history of clinically significant abnormal laboratory findings ≤ 14 days prior to enrollment, including: • Neutropenia (<1000 neutrophils/mm^3) • Thrombocytopenia (<100,000 platelets/mm^3) • AST, ALT, alkaline phosphatase, or bilirubin > 1.5 × ULN • Serum creatinine >2.0 mg/dL 8. Evidence of current clinical instability including the following: • Sustained systolic blood pressure <100 mmHg or cardiogenic shock • Acute pulmonary edema or severe congestive heart failure (CHF). Severe CHF is defined as NYHA Class IV • Suspected acute myocarditis, pericarditis, endocarditis, or cardiac tamponade • Suspected dissecting aortic aneurysm • Hemodynamically significant valvular heart disease, hypertrophic cardiomyopathy, restrictive cardiomyopathy, or congenital heart disease

	9. History of stroke or transient ischemic attack within 6 months prior to procedure 10. Active peptic ulcer or upper gastrointestinal bleeding within 6 months prior to procedure 11. History of bleeding diathesis or coagulopathy or refusal of blood transfusions 12. Other pathology such as cancer, known mental illness, etc., which might, in the opinion of the Investigator, put the patient at risk or confound the results of the study 13. Unable or unwilling to comply with the protocol 14. Currently participating in an investigational drug or device study that has not completed the primary endpoint or that clinically interferes with the current study endpoints; or requires coronary angiography, intravascular ultrasound, or other coronary artery imaging procedures *Angiographic exclusion criteria* 15. Occlusion involves segment within previous stent ("in-stent occlusions") 16. Extensive lesion-related thrombus (TIMI thrombus grade 3 or 4) 17. Previous stenting (drug-eluting or bare metal) in the target vessel unless the following conditions are met: • It has been at least 9 months since the previous stenting • Target lesion is ≥15 mm away from the previously placed stent • Previously stented segment (stent plus 5 mm on either side) has no more than 40% diameter stenosis, based on visual estimate 18. Target vessel has other lesions proximal to the total occlusion identified with > 75% diameter stenosis based on visual estimate; exception: planned stenting of a lesion proximal to the target lesion that can be covered by a single stent (i.e., tandem lesions) is acceptable
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1.0 ABBREVIATIONS

The following is a list of abbreviations used in the body of this document. Abbreviations solely used in tables (e.g., table headers) are described in the table footer and are not included below.

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

2.0 INTRODUCTION

Chronic total occlusions (CTO) are complex lesions that are relatively common in patients undergoing coronary angioplasty (Patel 2013) and present a challenge in achieving total coronary revascularization (Christofferson 2005; Fefer 2012). CTOs are defined as complete occlusions of a coronary vessel evolving for more than three months (Stone 2005). Current treatment options include bypass surgery, percutaneous revascularization, or continued medical therapy alone (Fefer 2012), and it has been shown that incomplete revascularization is associated with negative long-term clinical outcomes (Farooq 2013).

Studies have shown the prevalence of CTOs to range from 18-52% in patients with coronary artery disease (CAD) undergoing coronary angiogram, depending on the definition used for CAD (> 50% vs. ≥ 70% vessel diameter stenosis) (Christofferson 2005; Fefer 2012). Despite the prevalence of CTOs, a significant portion go untreated, which highlights the complexity of the treatment and the perception of increased risk by operators (Fefer 2012; Christofferson 2005; Grantham 2009). Historical technical success rates range from 60-70% with the antegrade approach (Joyal 2010), however recent improvements in technology and procedural techniques have increased successful procedure rates (Joyal 2010). Innovative guidewire methods including retrograde and dissection re-entry techniques have become essential complements to the traditional antegrade approach (Joyal 2012).

Benefits from successful CTO revascularization include alleviation of symptoms, avoidance of coronary artery bypass graft (CABG) surgery, improved left ventricular function, and potentially better survival rates. For a CTO to be successfully treated, there needs to be technical success and an absence of complications (Joyal 2010; Grantham 2009).

Teleflex has developed a series of guidewires and catheters that are being studied under this protocol for the intended use of facilitating the safe and effective crossing of *de novo* CTOs and placement of conventional guidewires beyond the lesion via either a true lumen or subintimal pathway. The Teleflex study devices include the GuideLiner® V3 catheter (hereafter referred to as “GuideLiner catheter”), TrapLiner® catheter, Turnpike® catheter, and a series of five coronary guidewires (Spectre™ guidewire, R350™ guidewire, Raider™ guidewire, Warrior™ guidewire, and Bandit™ guidewire). All study devices are currently 510(k) cleared for non-CTO indications.

3.0 REGULATORY CLASSIFICATION

All study devices are currently 510(k) cleared for non-CTO indications, as shown in **Table 1**. The data captured in this study will be used to support U.S. Food and Drug Administration (FDA) 510(k) clearance for CTO indications.

Table 1: Study Device Regulatory Clearance

Study Device	510(k) Number	Clearance Date
GuideLiner catheter	K172090	10/20/17
TrapLiner catheter	K180088, K161901	4/4/18, 2/3/17
Turnpike catheter	K151981, K142065	8/13/15, 11/25/14
Spectre guidewire	K163444	1/6/17
R350 guidewire	K151234	11/18/15
Raider guidewire	K173532	12/15/17
Warrior guidewire	K180128	2/16/18
Bandit guidewire	K181647	7/20/18

4.0 TREATMENT DESCRIPTION

4.1 Device Description

The Teleflex study devices include the GuideLiner catheter, TrapLiner catheter, Turnpike catheter, and a series of five coronary guidewires (Spectre, R350, Raider, Warrior, and Bandit). A description of each device is provided below. Investigational Instructions for Use (IFU) are provided in **Appendices A-H**.

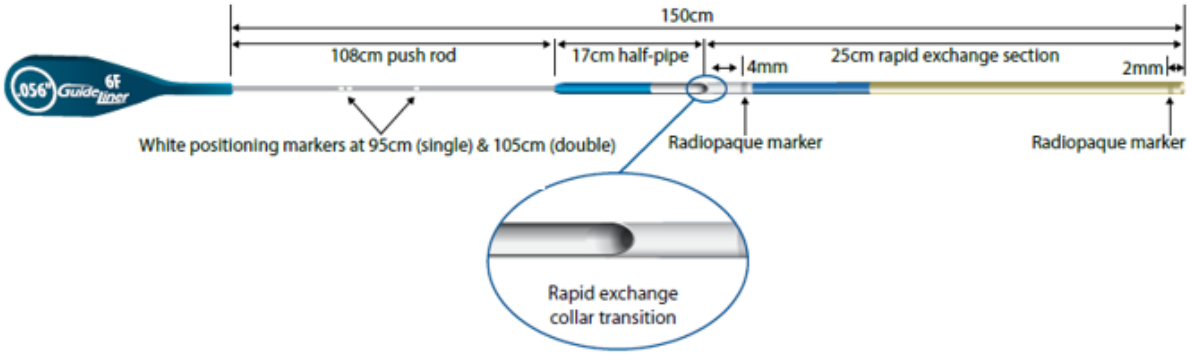
4.1.1 Guide Extension Catheters

Either the GuideLiner or TrapLiner catheter should be used in all cases in which a guide extension catheter is needed; see justification in Section 4.1.4.

GuideLiner Catheter

The GuideLiner V3 catheter (**Figure 1**) is a rapid-exchange guide extension catheter designed for use in the coronary and peripheral vasculature. It is available in five sizes – 5F, 5.5F, 6F, 7F, and 8F. All sizes of the GuideLiner V3 catheter have a 150 cm working length, consisting of a 125 cm long stainless steel pushwire shaft followed distally by a 25 cm long full-round, silicone-wiped guide extension segment. The distal 17 cm of the 125 cm pushwire shaft is covered with a semi-circular shaped polymer that meets the proximal end of the full-round guide extension segment. The GuideLiner V3 catheter has two platinum-iridium marker bands; the distal marker band is located at the distal tip and the proximal marker band is located near the collar. The GuideLiner V3 catheter also has two positioning marks located 95 cm (single mark) and 105 cm (double mark) from the distal tip.

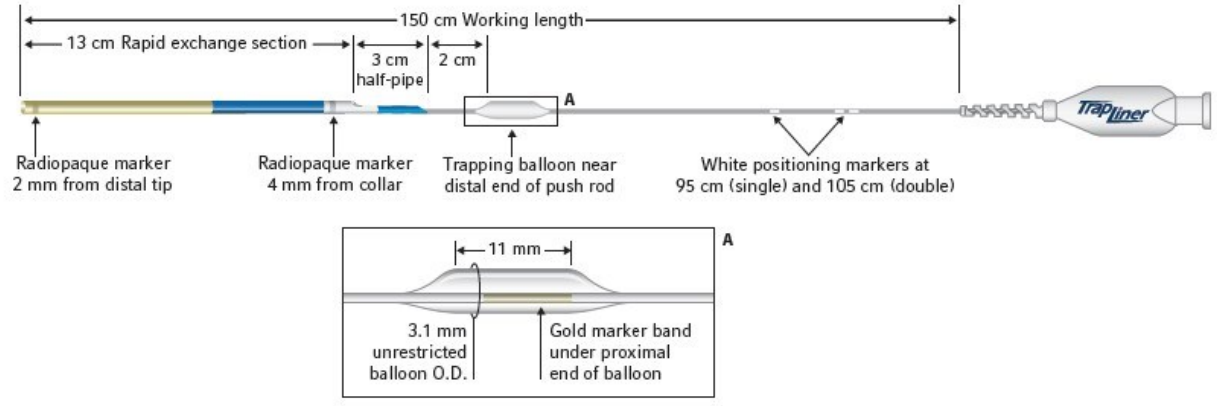
Figure 1: GuideLiner Catheter



TrapLiner Catheter

The TrapLiner catheter (**Figure 2**) is a rapid-exchange guide extension catheter with a trapping balloon on the distal end of the pushrod. It is available in 6F, 7F, and 8F sizes. The stainless-steel pushrod is covered on the distal end by a semi-circular polymer ("half-pipe") and transitions to a hydrophilic coated full-round polymer guide extension section. There are two radiopaque marker bands on the guide extension segment, one on the distal tip and one on the collar. The trapping balloon is located proximal to the half-pipe and has a single radiopaque gold marker under the proximal end of the balloon.

Figure 2: TrapLiner Catheter



4.1.2 Turnpike Catheter

At least one model of the Turnpike catheter must be used in each procedure; see justification in Section 4.1.4.

The Turnpike catheter is single lumen and designed for use in the coronary and/or peripheral vasculature. The catheter shaft is constructed with an outer polymer layer that encapsulates a braid and a dual-layer coil. The distal 60 cm of each catheter has a hydrophilic coating.

The Turnpike catheter is available in four design versions (**Figure 3**):

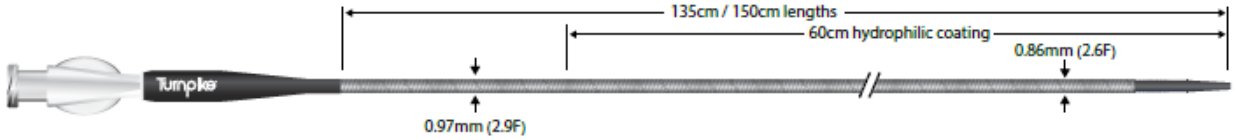
- **Turnpike catheter** (long, flexible, radiopaque distal tip): Model 5642 and 5643

- **Turnpike LP catheter** (lower profile & increased flexibility): Model 5638 and 5639
- **Turnpike Spiral catheter** (adds an outer coil onto the distal shaft for additional rotational advancement): Model 5640 and 5641
- **Turnpike Gold catheter** (outer coil on the distal shaft and a gold-plated, stainless steel, threaded distal tip): Model 5621 and 5622.

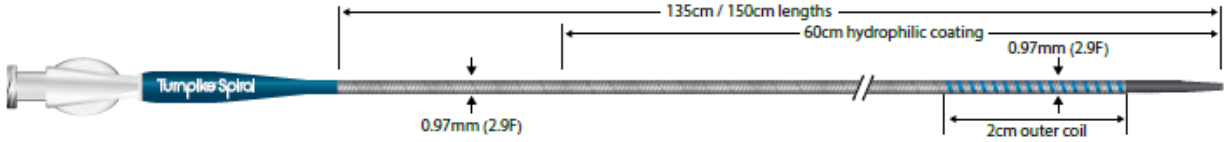
Each configuration is available in 135 cm and 150 cm lengths.

Figure 3: Turnpike Catheters

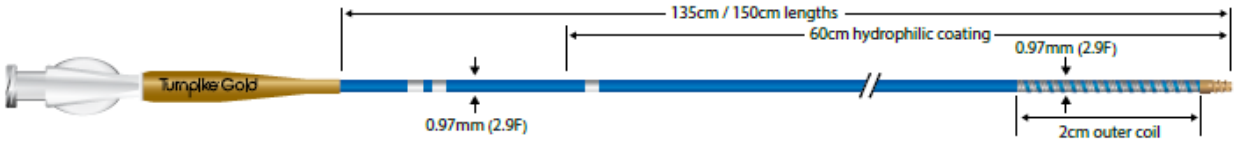
Turnpike Catheter



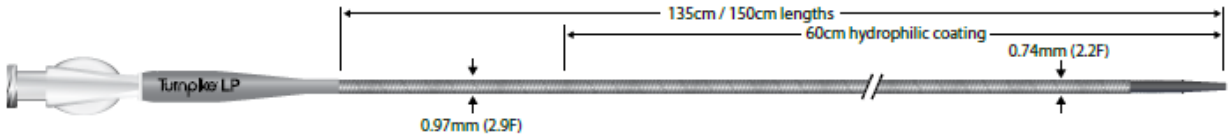
Turnpike Spiral Catheter



Turnpike Gold Catheter



Turnpike LP Catheter



4.1.3 Guidewires

At least one investigational guidewire must be used in each procedure. To ensure adequate representation of each guidewire in the study analysis, each of the following four guidewire devices should be used in a minimum of 20 subjects: Spectre, Raider, Warrior, and Bandit. The R350 guidewire should be used for all retrograde cases for which wire externalization is performed. Sites must promptly provide device use data on the applicable electronic case report forms (eCRF) after each enrollment so that the Sponsor/CRO can appropriately monitor usage throughout the enrollment period.

Spectre Guidewire

The Spectre guidewire is a nitinol and stainless-steel guidewire with a 0.014” diameter and straight shapeable tip. It is available in standard (Model 7386) and extended (Model 7387) lengths. The distal 25 cm of the guidewire has a spring coil with a 3 cm platinum coil on the distal tip that is visible under fluoroscopic methods. The distal 42 cm of the guidewire has a hydrophilic coating and the proximal portion has a polytetrafluoroethylene (PTFE) coating. Model 7386 has a modified proximal end to allow for guidewire extension.

Raider Guidewire

The Raider guidewire is a stainless-steel core guidewire with a maximum outer diameter of 0.014” and a straight, shapeable tip. It is available in standard and extended lengths. The standard length is compatible with a guidewire extension. The distal portion of the guidewire includes a radiopaque coil and is covered with a polymer jacket and hydrophilic coating. The proximal portion has a PTFE coating. It is available in standard (Model 7448) and extended (Model 7449) lengths.

Warrior Guidewire

The Warrior guidewire is a 0.014” diameter stainless steel core guidewire with a 0.009” diameter tapered distal tip. The distal 20 cm of the guidewire has a spring coil, of which the distal 2.5 cm is visible under fluoroscopic methods. The guidewire has a straight shapeable tip with a tip load of 14 grams. The distal portion of the guidewire has a hydrophilic coating and the proximal portion has a PTFE coating. It is available in standard (Model 7388) and extended (Model 7389) lengths. The proximal end of the standard version has a guidewire extension feature

Bandit Guidewire

The Bandit guidewire is a 0.014” diameter stainless steel core guidewire with a 0.008” diameter tapered distal tip. It is available in standard and extended lengths. The standard length (Model 7444) is compatible with a guidewire extension. The distal portion of the guidewire includes a radiopaque coil and is covered with a polymer jacket and hydrophilic coating. The proximal portion has a PTFE coating. It is also available in an extended length (Model 7445).

R350 Guidewire

The R350 guidewire (Model 7390) is 350 cm in length with a 0.013” maximum outer diameter (O.D) (0.012" nominal O.D.). It is composed of a nitinol alloy mandrel with a straight, radiopaque 5 cm gold-coated tungsten coil distal tip. The proximal 150 cm of the R350 guidewire has a PTFE coating, while the distal 200 cm has a hydrophilic coating.

4.1.4 Justification for Minimum Number of Device Uses

CTO patient populations often have different characteristics that cannot be entirely predicted, such as overall patient anatomy, lesion complexity, morphology, and calcification; therefore, it would not be appropriate to dictate in how many subjects each investigational device will be utilized, especially taking into consideration that Investigators will have an entire CTO toolbox at their disposal. While investigational devices are one component of the toolbox, other commercial devices play different roles and will also be necessary for procedural success.

Specifically considering the Turnpike catheter, each model has specific characteristics to address challenges presented by a variety of CTOs (e.g., the Turnpike Gold and Spiral catheters are generally used in more heavily calcified lesions).

Due to the different patient characteristics and device characteristics outlined here, minimum sample sizes have not been established for the GuideLiner or TrapLiner catheters, individual Turnpike catheter models, or the R350 guidewire.

As an alternative to establishing minimum sample sizes for these study devices, the following device use guidelines are provided to ensure adequate representation of each device in the study analysis:

- The GuideLiner catheter or TrapLiner catheter should always be used when any guide extension is necessary for completion of a study PCI procedure
- At least one model of the Turnpike catheter must be used in all cases
- The R350 guidewire should be used for all retrograde cases for which wire externalization is performed

4.2 Principle of Operation / Mechanism

The principles of operation for the study devices are summarized in **Table 2** below.

Table 2: Principles of Operation

Device Name	Principles of Operation
GuideLiner catheter	The GuideLiner catheter is delivered inside a guide catheter and over a guidewire to access discrete regions of the coronary and peripheral vasculature. The stiffer proximal shaft of the GuideLiner provides pushability of the catheter through tortuous vessels and the floppy distal segment extends the working length of the guide catheter to facilitate placement of interventional devices in discrete regions of the vasculature.
TrapLiner catheter	The TrapLiner catheter is delivered inside a guide catheter and over a guidewire to access discrete regions of the coronary and peripheral vasculature. The stiffer proximal shaft of the TrapLiner provides pushability of the catheter through tortuous vessels and the floppy distal segment extends the working length of the guide catheter to facilitate placement of interventional devices in discrete regions of the vasculature. The TrapLiner catheter has a trapping balloon that, when inflated within the guide catheter, facilitates exchange of an interventional device while maintaining the position of the guidewire within the vasculature.
Turnpike catheter	The Turnpike catheters are delivered inside a guide catheter and over a guidewire to access discrete regions of the coronary and/or peripheral vasculature. They may be used to facilitate placement and exchange of guidewires and to subselectively infuse/deliver diagnostic and therapeutic agents.
Guidewires	Guidewires are advanced through guide catheters and microcatheters to access discrete regions of the coronary and peripheral vasculature.

4.3 Indications for Use

The indications for use for the study devices are shown in **Table 3** below. The data captured in this study will be used to support U.S. Food and Drug Administration (FDA) 510(k) clearance for CTO indications.

Table 3: Investigational Indications for Use

Device Name	Indications for Use
GuideLiner catheter	GuideLiner catheters are intended to be used in conjunction with guide catheters to access discrete regions of the coronary and/or peripheral vasculature, to facilitate placement of interventional devices, and to assist in crossing de novo coronary chronic total occlusions (CTO).
TrapLiner catheter	The TrapLiner catheter is intended for use in conjunction with guide catheters to access discrete regions of the coronary and/or peripheral vasculature, to facilitate placement of interventional devices, to facilitate the exchange of an interventional device while maintaining the position of a guidewire within the vasculature, and to assist in crossing de novo coronary chronic total occlusions (CTO).
Turnpike catheter	The Turnpike catheters are intended to be used to access discrete regions of the coronary and/or peripheral vasculature. They may be used to facilitate placement and exchange of guidewires, to subselectively infuse/deliver diagnostic and therapeutic agents, and to assist in crossing de novo coronary chronic total occlusions (CTO).
Guidewires	The Teleflex guidewires are intended for use in percutaneous procedures to introduce and position catheters and other interventional devices within the coronary and peripheral vasculature, including use in crossing or assisting in crossing de novo coronary chronic total occlusions (CTO).

Investigational IFUs are provided in **Appendices A-H**.

5.0 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 U.S. Food and Drug Administration (FDA) 510(k) clearance for CTO indications.

6.0 STUDY POPULATION

The population for this study is subjects with signs and/or symptoms considered typical of ischemic heart disease attributed to a *de novo* CTO (see **section 14.0** for definition) in a native coronary artery who are suitable candidates for a percutaneous revascularization.

7.0 ENDPOINTS

7.1 Primary Endpoint

The primary endpoint for the study is 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; defined in **section 14.0**).

7.2 Secondary Endpoints

The secondary endpoints for the study are:

- 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 (see **section 14.0** for MACE definition). 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 (see **section 14.0** for definition).

7.3 Statistical Methods

7.3.1 Analysis Datasets

All 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.

7.3.2 General Principles

Standard summary statistics will be calculated and reported; for continuous variables, statistics will include means, standard deviations, medians and ranges or interquartile ranges. Categorical variables will be summarized in frequency distributions.

All statistical analyses will be performed using SAS (version 9.4 or higher, SAS Institute Inc. Cary, NC), R (version 3.2 or higher, R Foundation for Statistical Computing, Vienna, Austria) or other widely accepted statistical or graphical software.

7.3.3 Analysis of 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).

The performance goal (PG) is derived from the literature on CTO crossing using similar endpoints and populations. Specific references and resulting analysis 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%.

7.3.4 Analysis of Secondary Endpoints

Secondary endpoints will be summarized and tabulated without formal hypothesis testing according to the general principles in **section 7.3.2** above.

7.3.5 Safety Analysis

Summary tables and listings will be provided for all reported adverse events, which will additionally be reported by seriousness and relatedness. Such summaries will be comprised of the number and percentage of subjects with an adverse event and the total number of such events. The proportion of subjects with events will be considered primary for analysis of adverse events.

7.3.6 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 in **section 7.3.3** above.

7.4 Statistical Analysis Plan

Refer to the separate Statistical Analysis Plan (SAP) for additional details on statistical design, method and analytical procedures. Any departure or deviation from these planned statistical methodologies will be documented and will include the statistical rationale for divergence.

8.0 STUDY DESIGN

8.1 Overall Design

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

8.2 Number of Sites & Subjects

The study will be conducted in up to 15 investigational sites in the U.S. This study will enroll up to 150 patients to provide adequate powering for hypothesis testing and an evaluable sample size of at least 135 patients. The study Sponsor and CRO will manage sites so that no single site enrolls more than approximately 20% of the total study enrollment.

8.3 Study Duration

Enrollment is expected to take approximately 12 – 18 months. Each study subject will actively participate in the study through hospital discharge. The overall study duration, from IRB approvals, first patient screening, to the final follow-up visit, data analysis and final report, is expected to be approximately 18 – 24 months.

8.4 Subject Eligibility Criteria

Eligible subjects have signs and/or symptoms considered typical of ischemic heart disease attributed to a *de novo* CTO (see **section 14.0** for definition) in a native coronary artery and are suitable candidates for a percutaneous revascularization.

8.4.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria:

General inclusion criteria

1. At least 18 years of age at the time of consent
2. Experiencing clinical symptoms considered suggestive of ischemic heart disease (e.g., chest pain or discomfort, heart failure) or has evidence of myocardial ischemia (e.g., abnormal functional study) attributed to the CTO target vessel and is scheduled for clinically indicated percutaneous revascularization
3. Subject is eligible and consents to undergo PCI procedure
4. Acceptable candidate for percutaneous transluminal coronary angioplasty (PTCA), stenting, and emergency CABG
5. Willing and able to sign a study Informed Consent Form (ICF) approved by a local or central Institutional Review Board (IRB)

6. Female subjects of childbearing potential must have a negative pregnancy test per standard of care for PCI and be practicing contraception

Angiographic inclusion criteria

7. A minimum of one *de novo* lesion with at least one target segment in a native coronary vessel meeting the definition of CTO (any non-acute total coronary occlusion fulfilling the angiographic characteristics consistent with high-grade native coronary stenosis (Thrombolysis in Myocardial Infarction (TIMI) score of 0 or 1) and estimated to be in duration of ≥ 3 months by clinical history and/or comparison with antecedent angiogram or electrocardiogram)

8.4.2 Exclusion Criteria

Subjects must not meet any of the following exclusion criteria:

General exclusion criteria

1. History of allergy to iodinated contrast that cannot be effectively managed medically
2. Evidence of acute myocardial infarction (MI) within 72 hours prior to the intended treatment defined as CK-MB greater than 3 times the upper limit of normal (ULN)
3. Previous coronary interventional procedure of any kind within 30 days prior to the procedure
4. Any contraindication to cardiac catheterization or to any of the standard concomitant therapies used during routine cardiac catheterization and PCI (e.g., aspirin, clopidogrel, unfractionated heparin)
5. Target lesion requires treatment with another device, after successful crossing with a study device, other than PTCA devices prior to stent placement
6. Atherectomy procedure is planned for the target lesion
7. Known history of clinically significant abnormal laboratory findings ≤ 14 days prior to enrollment, including:
   - Neutropenia (<1000 neutrophils/mm^3)
   - Thrombocytopenia (<100,000 platelets/mm^3)
   - AST, ALT, alkaline phosphatase, or bilirubin > 1.5 × ULN
   - Serum creatinine >2.0 mg/dL
8. Evidence of current clinical instability including the following:
   - Sustained systolic blood pressure <100 mmHg or cardiogenic shock
   - Acute pulmonary edema or severe congestive heart failure (CHF). Severe CHF is defined as NYHA Class IV.
   - Suspected acute myocarditis, pericarditis, endocarditis, or cardiac tamponade
   - Suspected dissecting aortic aneurysm
   - Hemodynamically significant valvular heart disease, hypertrophic cardiomyopathy, restrictive cardiomyopathy, or congenital heart disease
9. History of stroke or transient ischemic attack within 6 months prior to procedure

10. Active peptic ulcer or upper gastrointestinal bleeding within 6 months prior to procedure
11. History of bleeding diathesis or coagulopathy or refusal of blood transfusions
12. Other pathology such as cancer, known mental illness, etc., which might, in the opinion of the Investigator, put the patient at risk or confound the results of the study
13. Unable or unwilling to comply with the protocol
14. Currently participating in an investigational drug or device study that has not completed the primary endpoint or that clinically interferes with the current study endpoints; or requires coronary angiography, intravascular ultrasound, or other coronary artery imaging procedures

Angiographic exclusion criteria

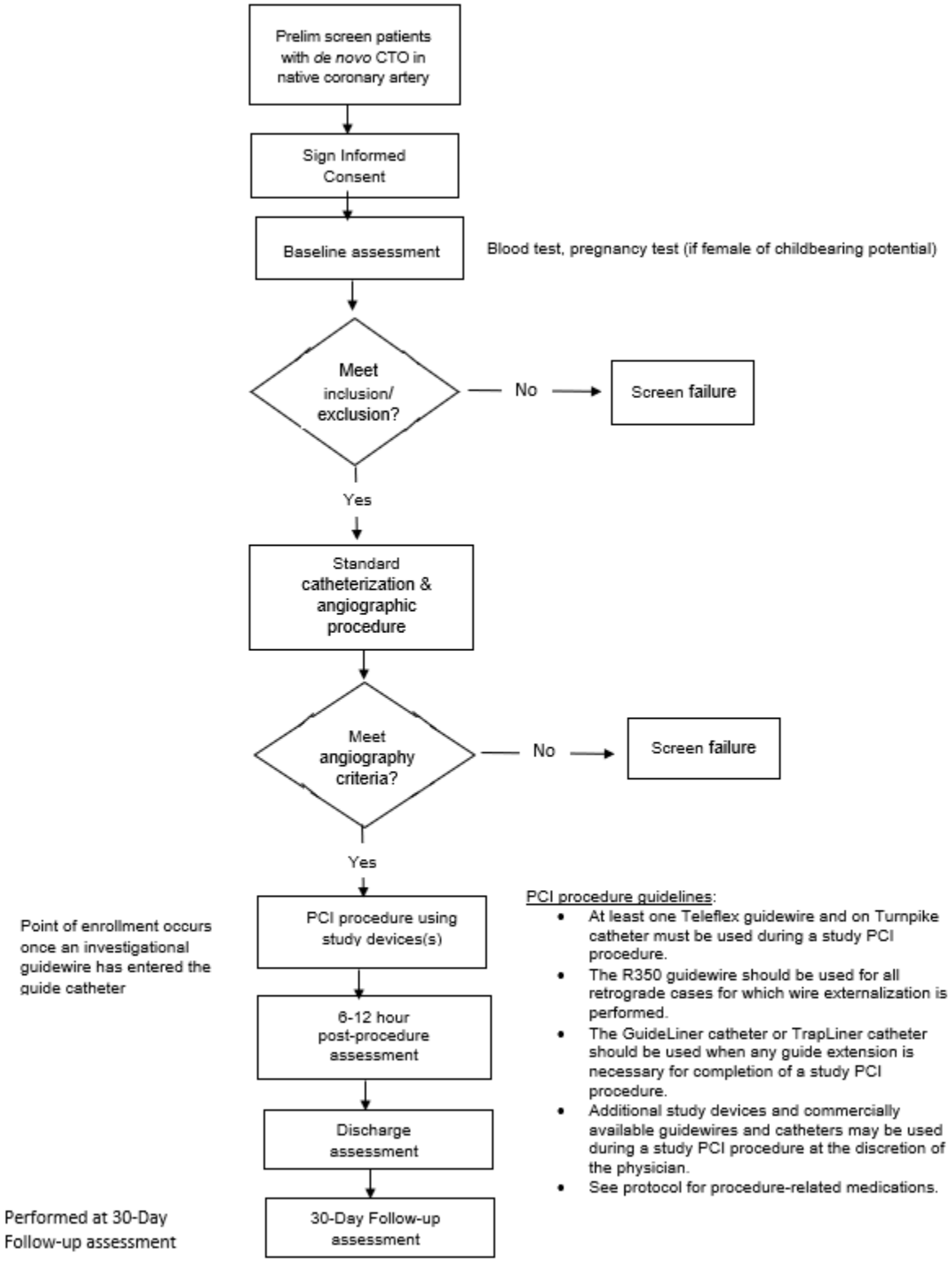
15. Occlusion involves segment within previous stent ("in-stent occlusions")
16. Extensive lesion-related thrombus (TIMI thrombus grade 3 or 4)
17. Previous stenting (drug-eluting or bare metal) in the target vessel unless the following conditions are met:
    - It has been at least 9 months since the previous stenting
    - Target lesion is ≥15 mm away from the previously placed stent
    - Previously stented segment (stent plus 5 mm on either side) has no more than 40% diameter stenosis, based on visual estimate
18. Target vessel has other lesions proximal to the total occlusion identified with > 75% diameter stenosis based on visual estimate; exception: planned stenting of a lesion proximal to the target lesion that can be covered by a single stent (i.e., tandem lesions) is acceptable

9.0 STUDY METHODOLOGY

9.1 Study Summary & Schema

Figure 4 summarizes the sequence of study assessments, procedures, and activities.

Figure 4: Study Flow Diagram



9.2 Screening

Screening is defined as the process of reviewing a patient's medical records against the study eligibility (non-angiographic inclusion and exclusion) criteria to determine if the patient is potentially eligible to enroll in the study. It is expected that the medical records will contain adequate information to determine if a patient meets most of these criteria. If the Investigator (or designee) determines the patient meets all non-angiographic inclusion criteria and no non-angiograph exclusion criteria (except criteria verified by blood testing after consent), they can be consented for study participation, after which all remaining non-angiographic eligibility criteria will be verified prior to the procedure. If any criteria are not met prior to the procedure, the patient will be considered a screen failure and will be tracked on the Screen Failure Log. Angiographic eligibility criteria will be verified at the time of procedure. If any angiographic eligibility criteria are not met, the patient will be considered a screen failure and recorded as such on the Screen Failure Log.

9.3 Informed Consent

Prior to enrolling patients in this study, the site will be required to have an Institutional Review Board (IRB) approved informed consent form (ICF). The contract research organization (CRO) must approve any modifications made to the Sponsor's template ICF prior to IRB submission.

Written informed consent will be obtained from the patient prior to the subject's participation in the study. The Investigator (or authorized designee) will explain the nature of the planned treatment and objectives of the study to the patient, allowing adequate time for the patient to read and review the consent form and to ask questions. The patient and the Investigator (or authorized designee) will sign and date the ICF.

The site will retain the original signed ICF in the subject's study records and will provide a copy of the signed ICF to the subject. The site will document the consent process (e.g., that the subject was consented, the date on which the consent was obtained, and that a copy of the signed ICF was given to the subject) in the subject's medical records.

Subjects will be informed of any new information that may make him/her change their mind about staying in the study. Subjects may be asked to sign a new ICF if this occurs.

9.3.1 Vulnerable Population

Sponsor is not anticipating enrollment of a vulnerable patient population (ref. ISO 14155:2011 section A.15).

9.4 Point of Enrollment & Numbering of Study Subjects

A patient will be considered enrolled as a study subject once an investigational guidewire has entered the guide catheter.

The site staff assigns the lowest available subject number progressing sequentially for each enrolled subject (e.g., 001, 002, 003). As soon as possible after a subject is enrolled, a member of the site's study team will notify the CRO, preferably by an entry in the database (EDC) or via email notification.

9.5 Schedule of Visits & Testing Requirements

Table 4 outlines the visits, visit windows, and testing requirements at each evaluation time point.

Table 4: Visits & Testing Requirements

Testing & Data Collection	Screening / Baseline	PCI Procedure *(Within 30 days of Screening Assessment)*	6-12 Hrs. Post-procedure	Discharge OR 18-24 Hrs. Post-procedure *(whichever comes first)*	30 days (± 7 days)
Inclusion and exclusion criteria	√				
Informed consent	√				
Demographics	√				
Medical & surgical history (within 14 days of procedure)	√				
Cardiac medication review	√	√		√	√
Pregnancy test (if female of child-bearing potential)	√				
Blood test (total CK and CK-MB)	√[1]		√	√	
Angiogram (pre- and post-PCI)		√			
PCI procedure		√			
Adverse event monitoring		√	√	√	√
Device deficiency assessment		√			

[1] Must be obtained within 72 hours of the procedure.

9.6 Subject Assessments & Study Procedures

Note: See **Section 14.0** for definitions of endpoint-related terms used in this section.

9.6.1 Baseline

The following standard of care evaluations and assessments will be performed at baseline:

- Demographics
- Medical and surgical history obtained within 14 days of the procedure (to include any previous catheterizations, vascular procedures/surgery, and concomitant diseases)
- Cardiac medication review (see **Section 14.0)**
- Blood test: Venous blood will be obtained for laboratory analysis; tests will include cardiac enzymes (total CK and CK-MB). Blood test results must be obtained within 72 hours of the procedure
- Pregnancy test (if female and of childbearing potential), per standard of care for PCI

After the baseline evaluations, the inclusion and exclusion criteria should be re-reviewed to ensure that the subject continues to be eligible for the study.

9.6.2 Pre-PCI Procedure Angiogram

Selection criteria for access approach (femoral or radial artery) will be at the discretion of the Investigator and will be based on a variety of clinical factors such as patient anatomy, vasculature, and other possible comorbidities.

Standard catheterization and angiographic procedures will be followed during this study and any adverse events that occur during and after the procedure will be collected. A pre-procedure angiogram of the target vessel will be completed per the Angiographic Core Laboratory Guidelines prior to any interventions on the CTO. Assessment of angiographic eligibility is based on a visual assessment of the pre-procedure angiogram.

9.6.3 PCI Procedure

The PCI procedure will be performed with the study device(s) following these guidelines:

- At least one Teleflex guidewire and at least one Turnpike catheter must be used during a study PCI procedure
- The R350 guidewire should be used for all retrograde cases for which wire externalization is performed.
- The GuideLiner catheter or TrapLiner catheter should be used when any guide extension is necessary for completion of a study PCI procedure
- Additional study devices and commercially available guidewires and catheters may be used during a study PCI procedure at the discretion of the physician

Post-procedure angiographic imaging of the CTO must be captured and performed per the instructions provided by the core laboratory and must be captured in a precise manner as was used for the pre-procedure images. Angiographic images of the CTO must be sent to the core lab per specified method.

If the subject is returned to the procedure room and a guiding catheter is reinserted and a dilatation is performed, this will be considered a repeat intervention.

Standard PCI procedural data will be collected on the CRFs such as:

- Vessel and lesion characteristics
- TIMI grade flow pre and post treatment
- Approach technique(s)
- Type and size of devices used
- The order in which guidewires were used and which guidewire was the crossing guidewire
- Procedural durations including start/end times
- Air Kerma (Gy) and total fluoroscopy time
- Procedure-related medications
- Adverse event assessment including perforation and dissection classifications
- Device deficiency assessment

See **Section 14.0** for procedure-related definitions and **Table 5** below for recommendations for procedure-related medications.

Table 5: Procedure-Related Medications Recommendations

Timepoint	Medication Recommendations
Pre-procedure	1. **Aspirin:** 100-325 mg non-enteric coated aspirin orally at least one hour and no more than 23 hours prior to procedure, or per hospital protocol. 2. **Clopidogrel:** 300 mg loading dose the day before the procedure or 600 mg the day of the procedure or sufficient existing steady state blood concentration, or per hospital protocol. If the patient had been taking Clopidogrel (75 mg/day) for three or more consecutive days prior to the procedure, the loading dose need not be given. **Note:** The use of glycoprotein IIb/IIIa inhibitors is not recommended.
Peri-procedure	• **Heparin** dose as required to maintain an activated clotting time (ACT)>250 seconds.
Post-procedure	• **Aspirin:** 100-325 mg administered daily, or per hospital protocol; AND • **Clopidogrel:** 75 mg by mouth daily or per hospital protocol; OR • **Ticagrelor:** 90 mg twice daily or per hospital protocol; OR • **Prasugrel:** 10 mg daily (5 mg if >75 years old or <60 kg weight), or per hospital protocol. Note: the use of glycoprotein IIb/IIIa inhibitors is not recommended.

9.6.4 6 – 12 Hours Post-Procedure

The following evaluations and assessments will be performed:

1. Blood test: total CK and CK-MB
2. Adverse event assessment

If CK-MB is > 3x the upper limit of normal (ULN), a series of CK-MB measurements may be performed per institutional standards starting from when the first elevation is noted. All CK and CK-MB values will be recorded on the appropriate eCRF.

9.6.5 18 – 24 Hours Post-Procedure / Discharge

The following evaluations and assessments will be performed at 18-24 hours post-procedure or directly prior to discharge, whichever occurs first:

1. Cardiac medication review (refer to **section 14.0** for definition)
2. Blood test: total CK and CK-MB
3. Adverse event assessment

If CK-MB is > 3x the upper limit of normal (ULN), a series of CK-MB measurements may be performed per institutional standards starting from when the first elevation is noted. All CK and CK-MB values will be recorded on the appropriate eCRF.

9.6.6 Thirty (30) Days Post-Procedure

The following evaluations and assessments will be performed at 30 days (±7 days) post-procedure via phone call and/or clinic visit and consist of:

1. Cardiac medication review (refer to **section 14.0** for definition)
2. Adverse event assessment

At the conclusion of this follow-up subjects will exit from this study via completion of the Study Completion eCRF. Subjects will continue to be followed by their physician per usual care.

9.6.7 Early Withdrawal/Premature Discontinuation of Subjects

Subjects may be withdrawn early from the study for several reasons including:

- Subject death
- Subject request for withdrawal (withdrawal of consent)
- Investigator decision, to be fully documented
- Safety reasons, as determined by Investigator, CEC, or FDA

If a subject is discontinued from the study early, a Study Completion eCRF must be completed describing the reason for early discontinuation. If a subject chooses to withdraw from the study and withdraws consent for disclosure of future information, no further evaluation(s) should be performed, and no additional data will be collected. The Sponsor may retain and continue to use any data collected prior to the withdrawal of consent.

10.0 MEASURES TO AVOID & MINIMIZE BIAS

The study has several measures that have been implemented to avoid and minimize bias including:

- Use of an independent CRO for study operations management, monitoring, and data management.
- Establishment of a Clinical Events Committee to independently review and adjudicate adverse events.
- Use of an independent angiographic core laboratory for systematic review of images removing any potential for Investigator bias.

10.1 Clinical Events Committee

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 following written CEC Adjudication Guidelines. Sites will be expected to provide supporting de-identified source documentation as requested to assist CEC adjudication.

10.2 Angiographic Core Laboratory

An angiographic core laboratory will be used to provide an unbiased assessment of angiographic imaging. The angiographic core laboratory will provide image acquisition and processing instructions to the sites. The angiographic core laboratory will follow its own Charter or similar procedure to systematize their image review in compliance with the study protocol.

11.0 ADVERSE EVENTS

11.1 Adverse Event Definitions

Refer to **Section 14.0** for adverse event definitions.

The following are not considered adverse events for this study:

- Any condition that is recorded as pre-existing on the Baseline CRF, unless there is a worsening of that condition in terms of nature, severity, or degree of incidence.
- Any normal expected symptoms associated with PCI unless the event involves a clinically significant change in severity or duration of symptoms or requires clinical intervention that is different from ordinary postoperative care. The following are examples of the normal responses to all PCI procedures and are not considered AEs:
  - Transient arterial spasm resolving spontaneously OR with medication only
  - Transient sinus bradycardia with heart rate ≤ 50 bpm, with no hemodynamic impact, and resolving spontaneously (Prophylactic placement and automatic activation of a cardiac pacer during this transient period does not constitute an intervention)
  - Minor discomfort or bruise at the arterial access place
  - Small amount of bleeding at point of arterial access that does not result in a hematoma > 5 cm, need for transfusion, or hemodynamic compromise
  - Side effects of standard-of-care medications

11.2 Adverse Event Collection & Documentation

Collection of adverse events will start when subjects are enrolled and will be assessed and reported throughout the study. Investigators must obtain all information available to determine the causality and outcome of the adverse event and to assess whether it meets the criteria for classification as a related serious adverse event requiring immediate notification. All adverse events will be followed until resolution or Investigator determination that the subject's condition is stable.

All reported adverse events will be documented on the Adverse Event CRF. Copies of de-identified source documentation that contain significant information related to the event, such as progress notes, consultations, nurse's notes, operative reports and subject summaries, etc. may be requested by the Sponsor, CRO, CEC and/or angiographic core lab as needed for evaluation and adjudication.

Device deficiencies will also be collected. If a device deficiency results in the subject experiencing any untoward medical occurrence, unintended disease or injury, or untoward clinical signs, these outcomes will be reported as an adverse event on an Adverse Event CRF. Any malfunctioning devices will be returned to the Sponsor by the Site for further evaluation.

In case of subject death, it is requested that a copy of the death certificate and a copy of the autopsy report, if applicable, be sent to the CRO. Any other source documents related to the death should also be provided to the CRO. If no source documents are available, the PI is required to describe the circumstances of the subject's death in written communication (e.g., letter, e-mail).

11.3 Adverse Event Reporting Timeframes

The Investigator is responsible for reporting serious adverse events to the IRB in accordance with the IRB's procedures. Unanticipated adverse device effects (UADEs) have special reporting requirements for both the Investigator and Sponsor, as described in 21CFR812.150:

- **Investigator Report:** If a subject experiences a UADE, the Investigator must notify the Sponsor and the reviewing IRB as soon as possible, but no later than 10 working days after the Investigator first learns of the effect.
- **Sponsor Report:** UADEs will be reported to the Food and Drug Administration (FDA), all reviewing IRBs, and participating Investigators as soon as possible, but no later than 10 working days after receiving notice of the UADE.

Sites will also follow regulations for reporting serious device-related injury and/or deaths by way of the MedWatch process (Medical Device Reporting [MDR] for Device User Facilities for FDA approved/cleared product). The FDA and Sponsor understand that FDA may receive duplicate reports of serious potentially related adverse events due to the clinical trial data collection process and the duplicate MDR reporting process. The FDA and Sponsor also understand that event information may be reported via the MDR process prior to Sponsor event monitoring and CEC adjudication.

11.4 Adverse Event Relationship

The Investigator and the CEC will assess the relationship of the adverse event to the device treatment or procedure as follows:

- **Definitely:** The adverse event follows a strong temporal sequence to the receipt (or attempted receipt) of the device treatment or procedure. This can include an adverse event that occurs after the study procedure.
- **Probably:** The adverse event follows a reasonable temporal sequence to the receipt (or attempted receipt) of the device treatment or procedure, and the possibilities of other factors, such as underlying and concomitant illness, concomitant medications, or concurrent treatment can be excluded.
- **Possibly:** The adverse event follows a reasonable temporal sequence from receipt (or attempted receipt) of the device treatment or procedure and the possibility of device

treatment or procedure involvement cannot be excluded. However, other factors such as underlying or concomitant illness, concomitant medications, or concurrent treatment are presumable.

- **Unlikely:** The adverse event has an improbable temporal sequence to the receipt (or attempted receipt) of the device treatment or procedure, or it can be reasonably explained by other factors, including underlying or concomitant illness, concomitant medications, or concurrent treatment.
- **Not Related:** The adverse event has no temporal sequence to the interventional procedure, the device treatment, or any user handling, or it can be explained by other factors, including underlying disease or concomitant illness, concomitant medication, or concurrent treatment.

Adverse events adjudicated by the CEC as *definitely* or *probably* will be considered related adverse events for data analytic purposes. Events adjudicated by the CEC as *possibly*, *unlikely* or *not related* will not be considered related adverse events for data analytic purposes.

All reported major cardiac adverse events, regardless of relationship, will result in a procedure failure for data analytic purposes. Refer to **Section 14.0** for definitions of MACE and procedure success.

12.0 RISK/BENEFIT ANALYSIS

12.1 Potential Benefits of Study Participation

There are no guaranteed benefits from participation in this study; however, it is possible that treatment with a study device may have the following benefits:

- Potentially lower-risk catheter-based revascularization of a coronary artery that may otherwise require surgical intervention via CABG
- Reduction in symptoms of CAD
- Improvement in quality of life

12.2 Alternative Treatment

There is no obligation for a patient to take part in this study. Alternative treatments may include:

- Surgical intervention via CABG
- Interventional procedure using commercially available CTO devices (e.g., Boston Scientific CrossBoss Catheter, Stingray LP catheter and Stingray Guidewire; Boston Scientific TruePath CTO Device; Asahi guidewires and/or Corsair microcatheter)

12.3 Potential Risks Associated with Study Participation

As with any surgical procedure, use of the study devices during PCI involves some risks. The potential risks or discomforts listed below may be associated with the study devices. Risks associated with the PCI procedure will be listed in the Site's procedure consent form used per

their standard of care. The list below includes possible risks associated with the use of the study devices in a CTO population.

The frequency and severity of adverse events can vary, and may necessitate additional medical intervention, including surgery.

Bleeding	Hypotension	Stent dislodgement
Cardiac arrest	Infection	Tachycardia
Cardiac tamponade	Inflammatory response	Thrombosis
CVA / stroke	Myocardial infarction	Vessel dissection
Death	Pericardial effusion	Vessel perforation
Embolism	Septal hematoma	Vessel rupture
Hematoma	Slow-flow / occlusion	Vessel spasm
Hypertension		

Additional possible risks from the evaluations required during this study (but not directly related to the use of the study devices) include:

Laboratory Testing Risks:

For blood tests, a sample will be taken by inserting a needle into a vein in the arm. Some risks of this procedure include fainting, infection, bruising, formation of a blood clot, pain, and/or bleeding at the site of the needle puncture.

12.4 Methods to Minimize Risks

A risk analysis has been conducted and risks have been minimized through appropriate design control and confirmed by pre-clinical bench and laboratory testing.

To mitigate the risks above, Teleflex will work with interventional cardiologists trained specifically in CTO revascularization techniques, train all study personnel, and provide device labeling that contains all appropriate information to treat the patient.

12.5 Risk-to-Benefit Rationale

The results from the risk analysis and risk mitigation measures, combined with commercial experience with study devices, support reasonable assurance of the safety and efficacy of the Teleflex study devices. The evidence supporting the safety and effectiveness of the Teleflex study devices is also based on a foundation of CTO PCI clinical investigations (reference Asahi Intecc NCT02379923; Kandzari 2018) and seven years of market experience with similar market-released CTO products (reference BridgePoint Medical System [now Boston Scientific] CrossBoss/Stingray K102725 (2011)). The evidence supports a clinical benefit to risk determination that is favorable for the Teleflex study devices.

13.0 ADMINISTRATIVE PROCEDURES

13.1 Records & Reports

13.1.1 Case Report Forms

A clinical trial database, commonly referred to as an electronic data capture (EDC) system will be used to collect study-required data on eCRFs. The Principal Investigator (PI) at the site is responsible for ensuring the eCRFs are accurate and completed in a reasonable timeframe. The PI is required to review and approve the eCRF on the appropriate page(s) to verify the completeness, accuracy, and authenticity of the recorded data.

13.1.2 Sponsor / CRO Study Records

The Sponsor and CRO are responsible for maintaining study records and reports per applicable ICH Good Clinical Practices (GCP), FDA regulations, ISO 14155, and applicable standard operating procedures and study specific-plans (e.g., Monitoring Plan, Data Management Plan, Training Plan, and Statistical Analysis Plan).

13.1.3 Investigator Study Records

The Investigator will maintain the following accurate, complete, and current records relating to their participation in the study as follows:

- All significant correspondence that pertains to the investigation.
- Records of each subject's case history and exposure to the investigational device. Case histories include the CRFs and supporting data including, for example, signed and dated ICFs and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. Such records will include:
    - Documents evidencing the informed consent process. The case history of each individual will document that informed consent was obtained at the appropriate time.
    - All relevant observations, including records concerning adverse device effects (whether anticipate or unanticipated), information and data on the condition of each subject upon entering, and during the course of, the investigation, including information about relevant previous medical history and the results of all diagnostic tests.
    - A record of the exposure of each subject to the investigational device, including the date and time of each use, and any other therapy.
- The protocol, with documents showing the dates and reasons for each deviation from the protocol.
- Signed Investigator Agreements, financial disclosure agreements, Investigator signature pages from the protocol, and curriculum vitae (CV).
- IRB approval documents including approval of the protocol, protocol amendments and ICF.

13.1.4 Investigator Reporting Requirements

Investigator reporting requirements are noted in **Table 6** below.

Table 6: Investigator Reporting Requirements

Report	Submitted To	Description
Unanticipated Adverse Device Effects (UADE)	Sponsor/ CRO & IRB	Notification within 10 working days after the Investigator first learns of the effect.
Device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate	Sponsor/ CRO	Notification within 5 working days after the Investigator first learns of the device deficiency that might have led to an SAE.
Serious Adverse Events (SAE)	IRB	Per IRB reporting requirements.
Withdrawal of IRB approval	Sponsor/ CRO	Notification within 5 working days of withdrawal.
Progress Report	Sponsor/ CRO & IRB	Periodic report detailing the progress of the study, occurring at least annually.
Deviations from protocol (CFR 812.150)	Sponsor/ CRO & IRB	**Emergency Use:** Notification must be made within 5 working days of the occurrence of an emergency deviation (made to protect the life or physical well-being of a subject). **Other:** If the deviation affects scientific soundness of the study or the rights, safety, or welfare of the subject (and is not an emergency), prior approval must be obtained from Sponsor the reviewing IRB, and FDA when required.
Failure to obtain informed consent	Sponsor/ CRO & IRB	Notification within 5 working days.
Final Report	Sponsor/ CRO & IRB	Submitted within 3 months after termination or completion of the investigation.

13.1.5 Record Storage & Retention

Refer to Clinical Research Agreement for trial data storage, access, and retention requirements.

13.2 Data Management

Correction of missing or unclear data will be requested as necessary throughout the study. The CRO may request additional information including source documentation as needed. The CRO will also be responsible for confirming the overall integrity of the data. Refer to the study-specific Data Management Plan for more details.

13.3 Device Accountability

All Teleflex study devices are FDA 510(k)-cleared and are being studied in this protocol for potential expanded indications. Because each of these devices are commercially available,

device accountability is not required. The Investigators will be trained to the investigational IFUs provided in **Appendices A-H**.

All commercial devices are labeled with reference and lot numbers. The specific reference and lot numbers will be recorded on the applicable eCRF when the device is used as part of the study.

13.4 Site Selection

Potential investigative sites are nominated for inclusion in the study based on their research history, expertise in treating CTO lesions, and familiarity with the Teleflex devices. The Sponsor and CRO will further assess each potential site to ensure the Investigators and his/her staff meet the minimum following criteria:

- The site has an interventional cardiologist that can act as principal Investigator
- The Investigators are qualified by experience and training
- The site has adequate research support staff with the availability to fulfill the clinical study requirements specified in the protocol
- The site has adequate access to CTO patients
- The site is not participating in another investigational study that is currently enrolling subjects with competing eligibility criteria; studies that have completed enrollment and are in the subject follow-up phase would not exclude the site from participation in the CTO study
- The Investigators are not on the FDA disqualified or debarred list

Additional details are specified in the study-specific Site Selection Questionnaires used to select eligible sites.

13.5 Site Training

Training of the clinical site personnel will be the responsibility of the study Sponsor and the CRO. Site personnel will be trained per the study-specific Training Plan. All site personnel will undergo training prior to performing any study-related procedures. All training will be documented. Existing site personnel who have been delegated new tasks and new site personnel will undergo training as designated in the Training Plan.

13.6 Site Monitoring

This clinical study will be monitored according to a study-specific Monitoring Plan that complies with GCP. Monitors will assess for appropriate study conduct and data integrity, including review of eCRFs and parity checks with the source documentation, worksheets, and hospital charts. At a minimum, the ICF and the ICF process, eligibility criteria, primary and secondary endpoint data, and adverse event data will be 100% monitored and compared to source documentation.

13.7 Institutional Review Board (IRB)

A central or institutional (“local”) IRB will review and approve this study for each participating site. The site must submit the protocol and ICF to the IRB and forward a copy of the written approval to the CRO. The study identification (study number, protocol title, and version), documents approved (e.g., protocol, ICF), and the date of the review should be clearly stated on the IRB approval documentation, and the approval must be signed by the IRB. The site will not be activated to enroll subjects until a copy of written and dated approval has been received by the CRO and other applicable study activation requirements (as outlined in the Monitoring Plan) are complete.

The site must submit any protocol or ICF amendments to the IRB and is required to forward a copy of the written approval to the CRO. An IRB approval of the amended document(s) must be obtained before implementation and before new subjects are consented to participate in the study using the amended ICF, if applicable. The IRB should also be informed of any event likely to affect the safety of subjects or the conduct of the study.

The ICF must be reviewed by the CRO prior to submission to the IRB for approval.

13.8 Protocol Deviations

A protocol deviation is defined as a circumstance in which the Investigator or other site personnel did not conduct the trial according to the protocol, applicable laws/regulations, or any study agreements (e.g., Clinical Research Agreement or Investigator Agreement).

Every attempt will be made to adhere to the protocol. However, should an Investigator be required to deviate from the protocol to protect the life or physical well-being of a study subject in an emergent circumstance, such notice will be given to the Sponsor or CRO as soon as possible, but no more than 5 working days from the date the emergency occurred. Except for an emergent circumstance, prior approval from the Sponsor and the IRB is required for any change in, or deviation from, the protocol as such changes may affect the scientific soundness of the protocol or the rights, safety, and welfare of study subjects.

Protocol deviations will be documented on the Protocol Deviation eCRF. Deviations are reportable to the Institution’s governing IRB during the annual reporting process, unless otherwise directed by the governing IRB requirements. Repeated serious protocol deviations will be closely monitored by the CRO/Sponsor. If excessive deviations or a failure to reduce deviations is noted, the Sponsor reserves the right to suspend study enrollment or terminate the site from the study until a sufficient system is in place at the site to reduce further deviations (21 CFR 812.46(a)).

13.9 Protocol Amendments

Changes to the protocol must be documented in a formal protocol amendment prior to implementation in the study. Amendments to the protocol will be initiated by the Sponsor or CRO and must be approved by the IRB prior to implementation at the site.

13.10 Study Termination

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).

If the study is terminated prematurely or suspended, the Sponsor will promptly inform all Investigators of the termination or suspension and the reason(s). The IRB will also be informed, either by the Sponsor or Investigator, and provided with the reasons(s) for the termination or suspension. If applicable, regulatory authorities will be informed.

The IRB may choose to discontinue the study at any Site for which they granted approval if the research study is not conducted in accordance with the IRB's requirements or the research study indicates unexpected serious harm to subjects.

13.11 Subject Confidentiality

All information and data sent to the CRO concerning a subject or their participation in this study will be considered confidential. The Sponsor, CRO, Monitors, CEC, IRB, and regulatory representatives will have access to these confidential files and have the right to inspect and copy all records pertinent to this study for data verification. All data used in the analysis and reporting of this study will be without identifiable references to a subject. Subject names and contact information will be available to the Sponsor, CRO, and Monitors during review of medical records. Subject names may be available to the core laboratory and the CEC as they review study-related radiographic images and source documentation. This information will be treated with adherence to professional standards of confidentiality. In addition, upon regulatory request, subject records shall be provided to U.S. regulatory agencies.

13.12 Statements of Compliance

This study is to be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki, as defined in the following U.S. and international standards for good clinical practice:

- International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice E6 (R2) (2016)
- U.S. Code of Federal Regulations (CFR) regarding clinical studies (21 CFR including parts 11, 50, 54 and 56 and 812) and HIPAA (45 CFR 164.508)
- ISO 14155: 2011

13.13 Publications & Public Disclosure

A publication committee will be formed to develop the publication plan and to oversee the development of the multi-center publication related to this study. Refer to the Clinical Research Agreement for publications and public disclosure requirements and conditions.

13.14 Study Contacts

Refer to the Sponsor Contact List for detailed contact information, including names, telephone numbers and email addresses for the Sponsor and CRO.

14.0 DEFINITIONS

Adverse device effect (ADE): An adverse event related to the use of an investigational medical device. *[ISO 14155:2011(E)]*

- This definition includes AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This definition also includes any event resulting from use error or from intentional misuse of the investigational medical device.

Adverse event (AE): Any untoward medical occurrence in a clinical investigation subject that does not necessarily have a causal relationship with the study treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product. An untoward event that is related to the study device may be referred to as an Adverse Device Event. [*ref. ICH E6(R2) Good Clinical Practice: Consolidated Guidance*].

Bleeding complications: Bleeding complications will be defined according to the GUSTO (Global Use of Strategies to Open Occluded Coronary Arteries) classification of severe, moderate, and mild bleeding events.

Severe or life-threatening: Either intracranial hemorrhage or bleeding that causes hemodynamic compromise and requires intervention.

*Moderate***:** Bleeding that requires blood transfusion but does not result in hemodynamic compromise.

Mild: Bleeding that does not meet criteria for either moderate or severe bleeding.

Cardiac death: Any fatal event not attributable to a noncardiac cause. [Kandzari, 2018]

Cardiac medication: Cardiac medications include:

- Antiplatelet medications such as aspirin, Clopidogrel, Prasurgrel, Ticlid, Ticagrelor
- Angiotensin converting enzyme (ACE) inhibitors
- Angiotensin receptor blockers (ARBs)
- Beta-blockers
- Calcium channel blockers
- Statins
- Other lipid lower agents
- Proton pump inhibitors
- Diuretics

- Anticoagulants
- Vasodilators

Chronic total occlusion (CTO): Any non-acute total coronary occlusion fulfilling the angiographic characteristics consistent with high-grade native coronary stenosis (TIMI score of 0 or 1) and estimated to be in duration of ≥ 3 months by clinical history and/or comparison with antecedent angiogram or electrocardiogram. [*aligns with Asahi Intecc CTO-PCI, NCT02379923; ref. Kandzari 2018*]

Crossing time: Time from initial CTO guidewire entered into guide to successful crossing. [definition provided by Dr. David E. Kandzari]

Device deficiency: Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. *[ISO 14155:2011(E)]*

- Note: Device deficiencies include malfunctions, use errors, and inadequate labelling.

Dissection Classification System [*NHLBI 1989 classification system*]**:**

- **Type A:** Minor radiolucent areas within the coronary lumen during contrast injection with little or no persistence of contrast after the dye has cleared
- **Type B:** Parallel tracts or double lumen separated by a radiolucent area during contrast injection, with minimal or no persistence after dye clearance
- **Type C:** Appear as contrast outside the coronary lumen (“extraluminal cap”) with persistence of contrast after dye has cleared from the lumen
- **Type D:** Spiral (“barber shop pole”) luminal filling defects, frequently with excessive contrast staining of the dissected false lumen
- **Type E:** Appear as new, persistent filling defects within the coronary lumen
- **Type F:** Dissections that lead to total occlusion of the coronary lumen without distal antegrade flow
- Note: Type E and F dissections may represent thrombus

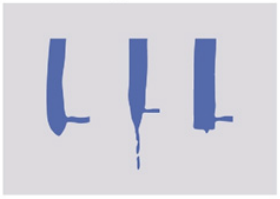
J-CTO Score [*Morino et al., 2011*]: Difficulty grading and time assessment tool for predicting successful guidewire crossing through CTO of native coronary lesions, via the J-CTO score sheet.

J-CTO SCORE SHEET

Version 1.0

Variables and definitions

Tapered / Blunt

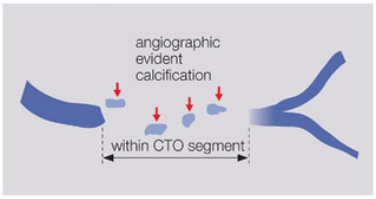


Entry with any tapered tip or dimple indicating direction of true lumen is categorized as "tapered".

Entry shape
☐ Tapered (0)
☐ Blunt (1)

point

Calcification

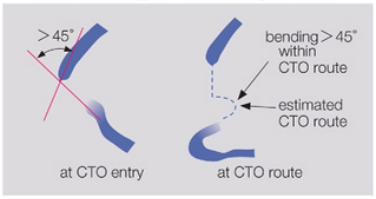


Regardless of severity, 1 point is assigned if any evident calcification is detected within the CTO segment.

Calcification
☐ Absence (0)
☐ Presence (1)

point

Bending > 45degrees

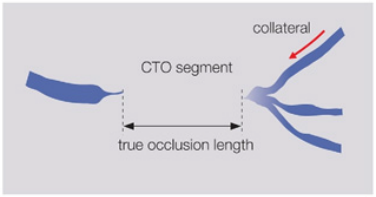


One point is assigned if bending > 45 degrees is detected within the CTO segment. Any tortuosity separated from the CTO segment is excluded from this assessment.

Bending > 45°
☐ Absence (0)
☐ Presence (1)

point

Occlusion length



Using good collateral images, try to measure "true" distance of occulusion, which tends to be shorter than the first impression.

Occl.Length
☐ <20mm (0)
☐ ≥20mm (1)

point

Re-try lesion

Is this Re-try (2nd attempt) lesion ? (previously attempted but failed)

Re-try lesion
☐ No (0)
☐ Yes (1)

point

Category of difficulty (total point)
☐ easy (0) ☐ Intermediate (1)
☐ difficult (2) ☐ very difficult (≥3)

Total
_____ points

Major adverse cardiac event (MACE): 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 ULN). Classification of an event as a MACE will be performed by the CEC. [*aligns with Asahi Intecc CTO-PCI, NCT02379923, which was based on Academic Research Consortium definitions; ref. Kandzari 2018*]

Myocardial infarction (MI): Q-wave or non-Q-wave, with CK-MB > 3 ULN [*aligns with Asahi Intecc CTO-PCI, NCT02379923, which was based on Academic Research Consortium definitions; ref. Kandzari 2018*]

NYHA Heart Failure Classification *[Dolgin et al, 1994]*:

I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Perforation Classifications [*Ellis et al., 1994*]**:**

- **Type I:** Extraluminal crater without extravasation.
- **Type II:** Pericardial or myocardial blush without contrast jet extravasation.
- **Type III:** Extravasation through frank (≥ 1mm) perforation.

Procedure success: 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). [*aligns with Asahi Intecc CTO-PCI, NCT02379923; ref. Kandzari 2018*]

Procedure times [*aligns with Asahi Intecc CTO-PCI, NCT02379923; ref. Kandzari 2018*]**:**

- **Procedure start time:** The first successful insertion of the guide catheter at an arteriotomy site is considered the start of the procedure.
- **Procedure end time:** The procedure is considered complete once the guide catheter is removed from the arteriotomy site.
- **Total study device procedure time:** The first successful insertion of a study device (catheter or guidewire) into the target artery is considered the start of the study device procedure. The study device procedure is considered complete once all study devices have been removed.

Serious adverse event (SAE): Any untoward medical occurrence that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, or results in persistent or significant disability/incapacity. *[ref: ICH E6(R2) Good Clinical Practice: Consolidated Guidance]*

- Note: An AE is considered “life-threatening” if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

Successful recanalization: Angiographic confirmation of crossing the chronic total occlusion and restoring blood flow to the affected area. [*aligns with Asahi Intecc CTO-PCI, NCT02379923; ref. Kandzari 2018*]

Target lesion: The CTO lesion being treated.

Technical success: Successful guidewire recanalization**.** [*Kandzari 2018*]

- Note: The technical success definition is applicable to investigational devices as at least one investigational guidewire must be used in every procedure.

TIMI: Thrombolysis in myocardial infarction grading scale. [*TIMI Study Group, 1985*]

TIMI 0 - no perfusion	There is no antegrade flow beyond the point of occlusion.
TIMI I - penetration without perfusion	The contrast material passes beyond the area of obstruction but “hangs up” and fails to opacify the entire coronary bed distal to the obstruction for the duration of the cineangiographic filming sequence.
TIMI II - partial perfusion	The contrast material passes across the obstruction and opacifies the coronary bed distal to the obstruction. However, the rate of entry of contrast material into the vessel distal to the obstruction or its rate of clearance from the distal bed (or both) are perceptibly slower than its entry into or clearance from comparable areas not perfused by the previously occluded vessel – e.g., the opposite coronary artery or the coronary bed proximal to the obstruction.
TIMI III - complete perfusion	Antegrade flow into the bed distal to the obstruction occurs as promptly as antegrade flow into the bed proximal to the obstruction, and clearance of contrast material from the involved bed is as rapid as clearance from uninvolved bed in the same vessel or the opposite artery.

TIMI Thrombus Grading Scale [*Gibson, 2001*]

Grade 0	No angiographic evidence of thrombus
Grade 1	Angiographic features suggestive of thrombus • Decreased contrast density • Haziness of contrast • Irregular lesion contour • A smooth convex meniscus at the site of a total occlusion • Suggestive, but not firmly diagnostic of a thrombus
Grade 2	Definite thrombus present in multiple angiographic projections • Marked irregular lesion contour with a significant filling defect – the thrombus’ greatest dimension is < ½ vessel diameter
Grade 3	Definite thrombus appears in multiple angiographic views • Greatest dimension from > ½ to < 2 vessel diameters
Grade 4	Definite large size thrombus present • Greatest dimension ≥ 2 vessel diameters

Grade 5	Definite complete thrombotic occlusion of a vessel • A convex margin that stains with contrast persisting for several cardiac cycles

Unanticipated Adverse Device Effect (UADE): 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 subjects. [*21 CFR 812.3(s)*]

15.0 REFERENCES

Asahi Intecc. The Asahi Intecc PTCA Chronic Total Occlusion Study (CTO-PCI). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2017-Jan-27. Available from: https://clinicaltrials.gov/ct2/show/NCT02379923.

Christofferson R, Lehmann K, Martin G, Every N, et al. Effect of Chronic Total Coronary Occlusion on Treatment Strategy. *Am J Cardiol*. May 2005;95(9):1088-1091.

Dolgin M, Association NYH, Fox AC, Gorlin R, Levin RI, New York Heart Association. Criteria Committee. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston, MA: Lippincott Williams and Wilkins; March 1, 1994.

Ellis S, Ajluni S, Arnold A, Popma J, et al. Increased Coronary Perforation in the New Device Era: Incidence, Classification, Management, and Outcome. *Circulation*. 1994;90:2725-2730.

Farooq V, Serruys P, Garcia-Garcia H, Zhang Y, et al. The Negative Impact of Incomplete Angiographic Revascularization on Clinical Outcomes and its Association with Total Occlusions: The SYNTAX (Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) Trial. *J Am Coll Cardiol*. 2013;61(3):282-294.

Fefer P, Knudtson ML, Cheema AN, Galbraith PD, et al. Current perspectives on coronary chronic total occlusions: the Canadian Multicenter Chronic Total Occlusions Registry. *J Am Coll Cardiol*. Mar 2012;59(11):991-997.

Gibson CM, de Lemos JA, Murphy SA, et al. Combination Therapy with Abciximab Reduces Angiographically Evident Thrombus in Acute Myocardial Infarction - a TIMI 14 Substudy. *Circulation.* 2001;103(21):2550-2554.

Grantham JA, Marso SP, Spertus J, House J, et al. Chronic Total Occlusion Angioplasty in the United States. *JACC Cardiovasc Interv*. June 2009;2(6):479-486.

Joyal D, Afilalo J, Rinfret S. Effectiveness of Recanalization of Chronic Total Occlusions: A Systematic Review and Meta-Analysis. *Am Heart J*. Jul 2010;160(1):179-187.

Joyal D, Thompson C, Grantham A, Buller C, et al. The Retrograde Technique for Recanalization of Chronic Total Occlusions: A Step-by-Step Approach. *JACC Cardiovasc Interv*. Jan 2012;5(1):1-11.

Kandzari D, Kini A, Karmpaliotis D, et al. Safety and Effectiveness of Everolimus-Eluting Stents in Chronic Total Coronary Occlusion Revascularization: Results from the EXPERT CTO Multicenter Trial. *JACC Cardiovasc Interv*. May 2015;8(6):761-769.

Kandzari D, Grantham JA, Karmpaliotis D, Lombardi W, et al. Safety and Efficacy of Dedicated Guidewire and Microcatheter Technology for Chronic Total Coronary Occlusion Revascularization: Principal Results of the Asahi Intecc Chronic Total Occlusion Study. *Coronary Artery Disease*. Dec 2018;29(8):618-623.

Morino Y, Abe M, Morimoto T, et al. Predicting Successful Guidewire Crossing Through Chronic Total Occlusion of Native Coronary Lesions Within 30 Minutes: The J-CTO (Multicenter CTO Registry in Japan) Score as a Difficulty Grading and Time Assessment Tool. *JACC: Cardiovascular Interventions.* Feb 2011;11(2):213-221.

Olivari Z, Rubartelli P, Piscione F, et al. Immediate Results and One-Year Clinical Outcome After Percutaneous Coronary Interventions in Chronic Total Occlusions: Data from a Multicenter, Prospective, Observational Study (TOAST-GISE). *J Am Coll Cardiol.* 2003;31:1672-1678.

Patel V, Brayton K, Tamayo A, Mogabgab O, et al. Angiographic Success and Procedural Complications in Patients Undergoing Percutaneous Coronary Chronic Total Occlusion Interventions: A Weighted Meta-Analysis of 18,061 Patients From 65 Studies. *JACC Cardiovascular Interventions*. Feb 2013;6(2):128-136.

Prasad A, Rihal C, Lennon R, et al. Trends in Outcomes After Percutaneous Coronary Intervention for Chronic Total Occlusions: A 25-Year Experience from the Mayo Clinic. *J Am Coll Cardiol.* Apr 2007;49(15):1611-1618.

Stone G, Kandzari D, Mehran R, Colombo A, et al. Percutaneous Recanalization of Chronically Occluded Coronary Arteries: A Consensus Document: Part I. *Circulation*. 2005;112:2364-2372.

TIMI Study Group. The Thrombolysis in Myocardial Infarction (TIMI) Trial – Phase I Findings. *N Engl J Med*. 1985;312:932-936.

Valenti R, Migliorini A, Signorini U, et al. Impact of Complete Revascularization with Percutaneous Coronary Intervention on Survival in Patients with at Least One Chronic Total Occlusion. *European Heart Journal.* 2008;29:2336-2342.

16.0 REVISION HISTORY

REV	Description of Change	Date
A	Initial release to FDA	11 Apr 2019
B	Release of IDE-approved copy. In section 7.3.3, updated mathematical expression of null hypothesis from H_0: μ < PG to H_0: μ ≤ PG upon recommendation from FDA. Added J-Score definition to section 14.0 and reference to section 15.0.	22 May 2019
C	Added 30-Day (± 7 days) assessment to collect 30-day MACE as part of secondary objectives for the study. Updated Figure 4 and Table 4 to reflect 30-Day assessment. Updated NCT number. Added abbreviations of CHF and NYHA to Abbreviations table. Updated exclusion criterion 7 in synopsis to reflect corresponding change in body of protocol. Updated exclusion criterion 2 to be consistent with protocol definition of an MI. Definition of Severe CHF added to exclusion criterion 8. References to “Angiographic Core Laboratory Guidelines” changed to “instructions provided by the core laboratory” Clarified reference to transient sinus bradycardia to heart rate ≤50 bpm. Added definition of New York Heart Association (NYHA) Heart Failure classification. Minor grammatical corrections to entire document.	04 Feb 2020

APPENDIX A: GUIDELINER CATHETER INVESTIGATIONAL INSTRUCTIONS FOR USE

APPENDIX B: TRAPLINER CATHETER INVESTIGATIONAL INSTRUCTIONS FOR USE

APPENDIX C: TURNPIKE CATHETER INVESTIGATIONAL INSTRUCTIONS FOR USE

APPENDIX D: SPECTRE GUIDEWIRE INVESTIGATIONAL INSTRUCTIONS FOR USE

APPENDIX E: RAIDER GUIDEWIRE INVESTIGATIONAL INSTRUCTIONS FOR USE

APPENDIX F: WARRIOR GUIDEWIRE INVESTIGATIONAL INSTRUCTIONS FOR USE

APPENDIX G: BANDIT GUIDEWIRE INVESTIGATIONAL INSTRUCTIONS FOR USE

APPENDIX H: R350 GUIDEWIRE INVESTIGATIONAL INSTRUCTIONS FOR USE