POST-MARKET STUDY PLAN

Randomized Clinical Study to Evaluate the Advance® Enforcer™ 35 Focal-Force PTA Balloon Catheter in Treatment of Arteriovenous Dialysis Access Circuit Stenosis

Global Clinical Number 17-04

Version: 17-04-02
Version Date: 03 Aug 2018

Global Sponsor: Cook Research Incorporated

STUDY PLAN SIGNATURE PAGE

Global Sponsor Contact:

I hereby acknowledge that the content presented in this study plan has been reviewed and agreed upon.

X Jennifer L. Kerr
Signature

09 Aug 2018
Date (DD Mon YYYY)

Jennifer L. Kerr, President
Printed Name

STUDY PLAN SIGNATURE PAGE

Principal Investigator:

I hereby acknowledge that I have read and understand this study plan and agree to comply with its contents and requirements.

X _____ _____
Signature Date (DD Mon YYYY)

_____
Printed Name

CONFIDENTIALITY STATEMENT

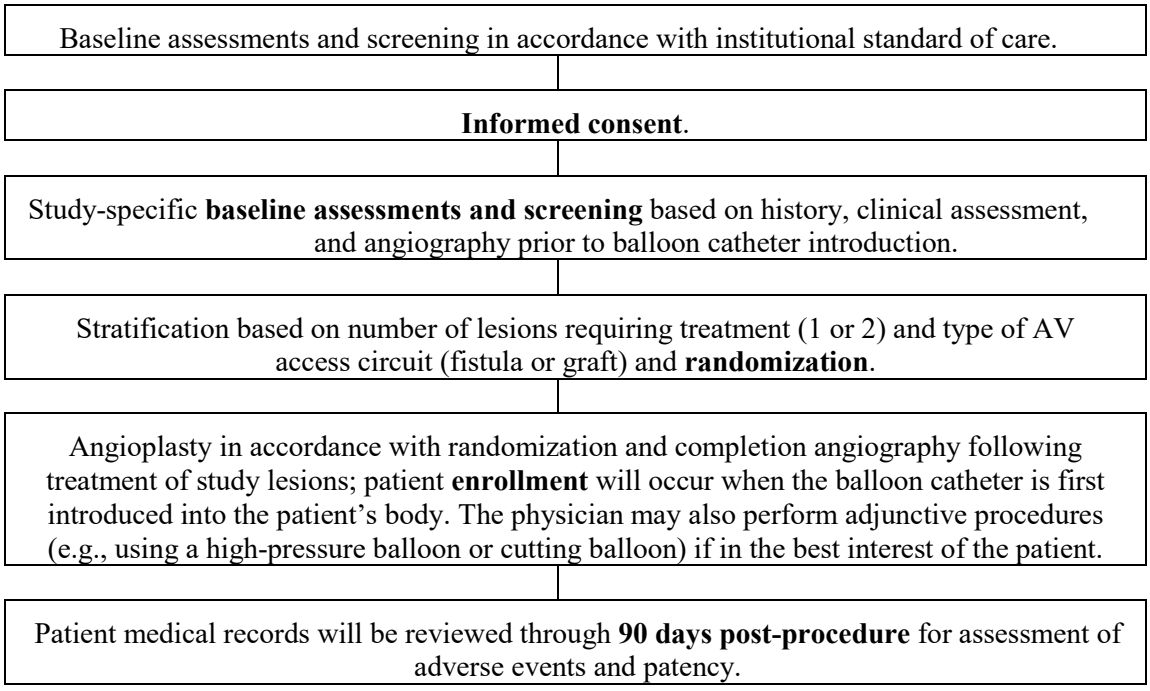
This document must be treated as a confidential document for the sole information and use of the clinical site personnel and the Institutional Review Board (IRB).

Table of Contents

Appendices

1.0 Study Plan Overview

Objective:	To evaluate the necessity of adjunctive therapy following treatment of stenoses of a mature native arteriovenous (AV) dialysis access circuit fistula or graft with the Advance® Enforcer™ 35 Focal-Force PTA Balloon Catheter (hereafter referred to as the Enforcer balloon) compared to stenoses initially treated with commercially available conventional balloon angioplasty.
Design of the clinical study:	Multicenter, stratified, randomized, controlled clinical study
Primary endpoint:	The primary endpoint is the percentage of lesions requiring adjunctive treatment immediately following the study procedure.
Number of patients:	Approximately 200 patients (at minimum 250 lesions)
Number of clinical sites:	Up to 10 clinical sites
Patient participation duration:	Patient's medical records will be reviewed through 90 days post-procedure.
Expected study duration:	Patient enrollment is expected to be completed within 1 year of study initiation. Total study duration (from study initiation through patient enrollment and follow-up) is expected to be 15 months.



2.0 Ethical Considerations and Regulatory Compliance

This clinical study will be conducted in accordance with the study plan, the ethical principles that have their origin in the Declaration of Helsinki, and the following:

- ISO 14155[a]

3.0 Objectives of the Clinical Study

The primary objective of this study is to evaluate the necessity of adjunctive therapy following treatment of stenoses of a mature native AV dialysis access circuit fistula or graft with the Enforcer balloon compared to stenoses initially treated with commercially available conventional balloon angioplasty.

4.0 Device Description

4.1 Intended Use

The Enforcer balloon is intended for percutaneous transluminal angioplasty (PTA) of lesions in peripheral arteries including iliac, renal, popliteal, infrapopliteal, femoral and iliofemoral as well as obstructive lesions of native or synthetic arteriovenous dialysis fistulae. This device is not for use in the cerebral or coronary vasculature.

For this study, the Enforcer balloon will be used in the treatment of obstructive lesions of native or synthetic arteriovenous dialysis fistula.

4.2 General Device Description

The Enforcer balloon is a double-lumen catheter with a balloon near its distal tip. Four polymer elements are incorporated into the balloon, which provide focal-force upon inflation. These elements will aid in opening lesions. Platinum/iridium, radiopaque markers are positioned on the shaft within the balloon to enable visualization of the catheter/balloon under fluoroscopy. The catheter is compatible with 0.035 inch (0.89 mm) wire guides.

---

[a] The study will not require strict adherence to all aspects of ISO 14155: 2011. Regarding section 6.8.1, Traceability of documents and data: A signature and date from a member of the investigation team will not be necessary for all source documentation. Regarding section 6.4.1, Adverse events and section 9.8, Safety Reporting: Adverse event reporting will be limited to those events listed in this Study Plan Section 9.6: Adverse Events. Event reporting may not occur until the patient's medical record review for the 90-Day Chart Review. Regarding section 4.7.4, Information to be provided to the subject: It may not be necessary for the patient to document their agreement to inform their personal physician of participation in the study.

Please reference the device for labeling information and the manufacturer's Instructions for Use (IFU) for the following:

- Detailed description of the device
- Instructions including storage and handling requirements, preparation for use, pre-use checks, precautions to be taken after use and disposal
- Summary of the necessary training and experience required for use of these devices
- Description of the procedures involved in the use of these device

4.3 Device Identification and Tracking

The study device is FDA cleared for use in the United States and will be obtained through standard commercial processes. Information regarding device dimensions and lot numbers will be reported through an electronic data capture system.

5.0 Background Information

The safety and performance of the Enforcer balloon were assessed through a series of nonclinical tests performed in accordance with verified methods and procedures to maintain the integrity of the results. The testing results provide reasonable assurance that the potential risks associated with the use of the device have been mitigated to an acceptable level. Additionally, conventional balloon angioplasty is a standard treatment for dialysis access dysfunction and several clinical evaluations have been performed and reported in literature, which assess safety and performance of angioplasty using different balloon technologies (e.g., conventional balloons, high pressure balloons, cutting balloons).[1]

A prospective, single-arm, single-center clinical evaluation of the Enforcer balloon was previously conducted to evaluate the treatment of AV access stenoses.[2] The study evaluated the treatment of 39 AV fistula lesions in 28 patients who were treated with 37 Enforcer balloons; patients were followed for 6 months post-procedure. Device success, defined as < 30% residual stenosis immediately following treatment was 64.1% (25/39). Similarly, 92.3% (36/39) of lesions were reduced to < 50% residual stenosis. Overall, treatment with the Enforcer balloon led to a reduction in the average percent diameter stenosis of the treated lesion from 66.3% pre-procedure to 23.7% post-procedure. The average maximum inflation pressure required was 12.3 atm. Only one lesion required adjunctive treatment following angioplasty with the study balloon, indicating that

clinically relevant luminal gains can be achieved with the study device alone, without the need for a high pressure balloon or other additional therapies.

Following the study procedure, all patients could resume normal dialysis. The Kaplan-Meier estimates for patency at 90 days and 6 months were 62.0% and 25.1%, respectively. The rate of access site complications were low (1/28; 3.6%). Overall, the data supported the safety of the Enforcer ballon for the treatment of stenotic lesions in mature native AV hemodialysis access circuits.

6.0 Risk Analysis and Risk Assessment

6.1 Risks and Foreseeable Adverse Events

Please reference the IFU for the following:

- Potential adverse events
- Warnings
- Precautions

In addition, participation in this clinical study is associated with the following risk:

- Release of personal information

6.2 Anticipated Clinical Benefits

Percutaneous transluminal angioplasty of a stenosed lesion in an AV access circuit could result in a resumption of normal hemodialysis.

6.3 Methods to Minimize Risks

Methods to minimize risk to patients include:

- Design of the device (as verified in nonclinical testing)
- Study design (e.g., monitoring of study conduct, limiting imaging requirements, eligibility criteria, informed consent)
- Conduct of the study at clinical sites with principal investigators qualified by training and experience
- Device will be used only by experienced investigators who have completed study training
- Study oversight by IRB
- Adverse event reporting as outlined in this study plan

- Capture, handling, and storage of the study data are done in compliance with applicable regulations to minimize the risk of release of any personal health information

The risks of the study have been minimized and the residual risks are considered acceptable because they do not outweigh the potential for benefit.

7.0 Design of the Clinical Study

7.1 Design of the Clinical Study

This multicenter, stratified, randomized, controlled clinical study will evaluate the performance of the Enforcer balloon compared to commercially available conventional balloons (defined as less than 25 atm rated burst pressure) in the treatment of stenoses of the AV dialysis access circuit.

This study will enroll approximately 200 patients at up to 10 clinical sites. Enrollment will end when it is determined a minimum of 250 lesions have been treated.

7.2 Study Design Rationale

A randomized clinical trial allows for the direct comparison of the rates of adjunctive treatment between the Enforcer balloon and other commercially available standard angioplasty balloons.

7.3 Duration of the Study and Patient Participation

Patient enrollment is expected to be completed within 1 year of study initiation. Total study duration (from study initiation through patient enrollment and follow-up) is expected to be 15 months.

A review of the patient's medical chart through 90 days after the study procedure will be conducted.

7.4 Measures to be Taken to Avoid or Minimize Bias

This study is designed as a stratified, randomized, controlled clinical trial to minimize bias in both assigning patients to treatments and in analyzing the results. Each clinical site is limited to a maximum number of patients (as described in Section 11.1: Sample Size) to minimize bias that may be introduced if the majority of patients are enrolled at

one or two clinical sites. In addition, the study will utilize uniform definitions for study endpoints.

7.4.1 Randomization

Once baseline angiography is complete and patient eligibility is confirmed, patients will be randomized into either the Enforcer balloon or conventional angioplasty group prior to treatment. At each study site, patients will be stratified for randomization based on the number of lesions requiring treatment (single lesion or two lesions) and type of AV access circuit (fistula or graft), then randomized to one of the treatment groups in a 1:1 ratio.

7.5 Endpoints

7.5.1 Primary Endpoint

The primary endpoint is the percentage of lesions receiving adjunctive treatment immediately following the study procedure (initial treatment with the Enforcer or conventional angioplasty balloon).

7.5.2 Secondary Endpoints

- Numeric rating scale (NRS) for pain experienced during study procedure balloon inflations
- Procedural cost
- Procedure times
- Maximum balloon pressure
- Device success
- Safety measures, including rupture, circumferential tears, and reintervention/patency

7.5.3 Additional Measures

- Anatomic success
- Clinical success
- Adverse events (refer to Section 9.6: Adverse Events for a list of reportable events)
- Primary patency through 90 days

7.5.4 Rationale for Endpoint and Additional Measures

The primary endpoint was chosen as it allows for the direct comparison of the rates of adjunctive treatment between the Enforcer balloon and other commercially available standard angioplasty balloons. The secondary endpoints and additional measures were chosen as applicable indicators of device effectiveness because of their similarity to those of interest in the literature and their similarity to other clinical studies.

7.6 Variables to be Measured to Demonstrate Achievement of Endpoints

The endpoints and additional measures will be assessed as described in Table 7.6-1.

Table 7.6-1. Assessment of Endpoints and Measures

Endpoint/Measure	Measure/Assessment
Use of adjunctive therapies	Procedural use of high-pressure balloons, cutting balloons, or stents following the study procedure (initial treatment with Enforcer or conventional angioplasty balloon)
Device success	Residual stenosis less than 30% within the treated lesion immediately after angioplasty with the study device (Enforcer or conventional angioplasty balloon)
Anatomic success	Residual stenosis less than 30% within the treated lesion following procedure (including any adjunctive therapy)
Procedural costs	Procedural charges and cost-to-charge ratio assessed after submission of UB-04 or CMS-1500 forms
Procedural time	Procedural time (defined as the time from needle entry for intervention to sheath withdrawal) will be assessed after angioplasty with the study device (Enforcer or conventional angioplasty balloon)
Balloon pressure	Maximum inflation pressure and duration
Numeric rating scale (NRS) for pain experienced during study procedure balloon inflations	Patient-reported pain assessment (scale of 0-10, where 0 indicates no pain and 10 indicates the worst possible pain)
Clinical success	Resumption of successful hemodialysis for at least one session from chart review through 90 days
Primary Patency	Uninterrupted patency of the AV hemodialysis access circuit assessed by reporting of reintervention or abandonment of dialysis

	access circuit from chart review through 90 days
Adverse events	Event information from chart review through 90 days • Refer to Section 9.6: Adverse Events, for a list of reportable events

8.0 Eligibility Criteria

Patient eligibility for enrollment will be based on existing information at the time of the procedure. Information obtained at a later date may contradict these criteria, but this will not be considered a deviation from the study plan.

Inclusion Criteria

A patient is suitable for inclusion in the study if the patient meets the following criteria:

1. A greater than 50% stenosis (when compared to the reference vessel diameter) of a mature native AV dialysis access circuit fistula or graft in the upper extremity[3]
2. Clinical or physiological abnormalities which indicate dialysis access dysfunction (e.g., decreased access blood flow, elevated venous pressure, decreased dialysis dose, abnormal physical exam)

Exclusion Criteria

Patients must be excluded from enrollment into the study if any of the following are true:

General Exclusion Criteria:

1. Less than 18 years old
2. Unwilling or unable to provide informed consent
3. Unwilling or unable to comply with the study schedule
4. Pregnant, lactating, or planning to become pregnant in the 3 months following enrollment
5. Simultaneously participating in an investigational drug or device study involving treatment of the AV dialysis access circuit in which the follow-up phase for that study's primary endpoint has not been completed 30 days or more prior to being enrolled in this study

Medical Exclusion Criteria:

6. Underwent any surgical or interventional procedure of the access circuit less than or equal to 30 days prior to the enrollment

7. Medical condition or comorbid conditions that would limit life expectancy to less than 6 months
8. Scheduled for a kidney transplant
9. Evidence of systemic or local infection associated with the AV dialysis access circuit
10. Uncorrectable bleeding diathesis or coagulopathy or will refuse blood transfusions
11. Stent or stent graft in or directly adjacent to the study lesion

Anatomic Exclusion Criteria:

12. Untreated hemodynamically significant central venous stenosis (>50%); (Central venous stenosis may be treated per standard of care during the study procedure)
13. Inability to cross a study lesion with a guidewire
14. Study lesion is greater than 4 cm in length (maximum of 4 cm per lesion and 8 cm total, if two lesions are treated)
15. Reference vessel diameter is less than 6 mm or greater than 10 mm
16. Presence of more than two distinct lesions (stenoses) in the AV dialysis access circuit

8.1 Patient Consent

Patients who meet all of the inclusion criteria and none of the exclusion criteria may be invited to participate in this study. Patients eligible for enrollment will have the clinical study explained to them, as well as potential risks and benefits of their participation in the study. Each patient, or legally-authorized representative (if approved by the IRB), who agrees to participate must sign and date an informed consent document prior to the procedure or any study-specific testing or assessments. If new information is obtained after a patient receives treatment with the device, patients who have not exited the study must be informed about the new information, and will be re-consented if required by the clinical site's IRB.

NOTE: Patients who have completed participation in this study may not be re-enrolled.

9.0 Methods

Refer to Appendix B for a schedule of events for the clinical study.

Data associated with assessment(s)/procedure(s) required by this study plan will be recorded on the appropriate electronic case report forms (eCRFs).

9.1 Pre-procedure

A pre-procedural clinical assessment will be completed and will include patient demographics and medical history. Baseline data will be collected and recorded on appropriate eCRFs. Baseline angiography should be performed prior to study enrollment to assess and document study lesion(s) characteristics including length, location, and percent (%) stenosis. Up to two distinct lesions can be treated within the dialysis access circuit. Pre-treatment for thrombosed dialysis access circuits may be performed (e.g., thrombectomy or thrombolysis) prior to enrollment in the study. Also, central venous lesions that require treatment (i.e., >50% stenosis) to meet eligibility criteria must be treated successfully prior to treatment of the study lesion. Successful treatment of the central veins is defined as less than 30% residual stenosis.

Once baseline angiography is complete and patient eligibility is confirmed, patients will be randomized as described in Section 7.4.1 into either the Enforcer balloon or conventional angioplasty balloon (defined as balloons with rated burst pressure of less than 25 atm) group prior to treatment.

Assessment(s) required to be completed prior to patient enrollment are summarized in Table 9.1-1.

Table 9.1-1. Pre-procedure requirements

Pre-procedure	
Assessment(s)/ Procedure(s)	Review study with the patient and obtain written informed consent
	Record demographics, medical history, and AV fistula/graft location
	Perform pre-procedural (baseline) angiography, recording lesion characteristics such as: • Lesion length, location, and % stenosis • Estimated reference vessel diameter
	If necessary, perform treatment of central venous stenosis, confirming residual stenosis less than 30%
	If necessary, perform pre-treatment for thrombosed access circuit
	Confirm ability to cross the study lesion(s) with a guidewire
	Randomize patient

If a subject does not qualify for study participation, the reason will be indicated on the appropriate eCRF.

9.2 Point of Enrollment

Patients are considered enrolled in the study once the balloon catheter is first introduced into the patient's body.

9.3 Study Procedure

PTA with either the Enforcer balloon or conventional angioplasty balloon will be performed and recorded in accordance with the manufacturer's IFU to achieve a residual stenosis < 30%. The balloon diameter may be chosen based on the recommendations in the IFU. If necessary, the balloon could be deflated, repositioned, and re-inflated to achieve a residual stenosis < 30%. Inflation details (e.g., maximum pressure and duration of inflations) will be recorded on an appropriate eCRF. Conventional angioplasty balloons are defined as those having a rated burst pressure less than 25 atmospheres. Completion angiography to assess percent residual stenosis of the treated study lesion(s) should be performed immediately following the study procedure (initial treatment with Enforcer or conventional angioplasty balloon) and prior to beginning any adjunctive procedures.

The physician may also perform adjunctive procedures (e.g., using a high-pressure balloon, cutting balloon, stent, or stent graft) if in the best interest of the patient. High-pressure angioplasty balloons are defined as those having a rated burst pressure greater than or equal to 25 atmospheres. The adjunctive procedure may be performed in accordance with the device manufacturer's IFU to achieve a residual stenosis < 30%. Completion angiography following any adjunctive procedures should also be performed. Any additional procedures performed will be documented on the appropriate eCRF.

All angiographic images and medical charges (i.e., UB-04 or CMS-1500) should be provided to the Sponsor on the appropriate eCRF. Total procedure time (defined as the time from needle entry for intervention to sheath withdrawal) as well as total procedural charges will be recorded on the appropriate eCRFs.

Type(s) and level(s) of sedation provided during the procedure will be recorded on the appropriate eCRF. A single assessment representing the pain associated with balloon inflations during the procedure is recommended to be recorded at or before the time of the patient's discharge assessment. Patients will be instructed to rate the pain they feel

using a numeric pain rating scale (0-10, where 0 indicates no pain and 10 indicates the worst possible pain). A summary of the procedure is given in Table 9.3-1 below.

Table 9.3-1. Procedure requirements

Procedure	
Assessment(s)/ Procedure(s)	Perform angioplasty according to study randomization
	Perform adjunctive procedures (as needed to achieve less than 30% residual stenosis, or if in the best interest of the patient) • If applicable, an additional completion angiography should be performed
	Record lesion treatment information on the appropriate eCRF, such as: • Post-treatment lesion % stenosis • Balloon information, including inflation(s), duration(s), and maximum balloon pressure(s)
	Complete patient-reported pain assessment
	Provide total procedural charges

9.4 Follow-up

Patient medical records will be reviewed through 90 days post-procedure for assessment of adverse events and patency (including reintervention or abandonment of the AV dialysis access site). Adverse event reporting will be limited to those events listed in Section 9.6: Adverse Events. Events occurring after 90 days post-procedure will not be collected. Clinical success will be determined, and is defined as resumption of successful dialysis for at least one session. The follow-up requirements are summarized in Table 9.4-1.

Table 9.4-1. Follow-up requirements

90 Day Follow-up	
Timing	Through 90 days following the study procedure
Type	Chart Review
	Record if patient received at least one successful hemodialysis treatment after the study procedure
	Record adverse events (including, but not limited to, reintervention or abandonment of the study access circuit; refer to section 9.6: Adverse events for a list of reportable events)

9.5 Reintervention

Patients requiring a reintervention within the study lesion may be treated in accordance with the institution's standard of care. Treatment information will be recorded on the appropriate eCRF.

9.6 Adverse Events

The following adverse events, occurring after the point of enrollment until the last day of patient participation, are to be reported to the sponsor using the appropriate eCRF:

- Events with potential relationship to the study device or study procedure
- Serious Adverse Events
- Restenosis or occlusion resulting in a reintervention or abandonment of AV dialysis access circuit

Information regarding occurrence of adverse events (including onset date, end date, date of awareness, event description, treatment, and whether the device or procedure contributed to the event) will be captured throughout the study and recorded on the appropriate eCRF.

Sites are responsible for following their normal reporting process (e.g., to manufacturer, to regulatory authority) for commercially available devices.

The sponsor is responsible for reporting events to the reviewing IRB(s) and principal investigator(s) as required according to applicable regulations/standards/policies.

10.0 Participation Endpoints of the Study

A patient's participation in the study will end after any of the following:

- Patient withdrawal (patient- or investigator-initiated)
- Medical records determined to be unobtainable for chart review
- Early termination of the study
- Patient death
- Completion of 90-Day chart review

After a patient exits the study for any reason (e.g., withdrawal, records determined to be unobtainable, study closure, or study completion), no additional data will be collected. Information up to the date of the participation endpoint will be provided to the Sponsor during the 90-Day chart review.

10.1 Patient Withdrawal

A patient may decide to withdraw from the study at any time either before or after undergoing the study procedure without prejudice or loss of care. The principal investigator may also decide to withdraw the patient from the study at any time based on medical judgment. If a patient is withdrawn, a medical chart review will be conducted through and including the date of withdrawal. In all instances of withdrawal, data collected up to the time of patient withdrawal will be submitted and will include the reason why the patient has been withdrawn from the study. Any data collected on the patient up to the point of withdrawal may be used in the study.

10.2 Early Termination or Suspension of the Clinical Study

Any decision to suspend enrollment or terminate the clinical study either completely or at multiple clinical sites will be made by the sponsor. The sponsor or the IRB may decide to suspend enrollment or terminate the study at an individual clinical site. Reasons for early termination or suspension of a study (or at one or more sites) may be due to safety concerns, effectiveness concerns, ethical concerns, alterations in accepted clinical practice, clinical site performance, or organizational issues. In the event of clinical site or study closure, all patients who have received the study treatment will be followed for 90 days following the study procedure.

The principal investigator-required notifications/reports are described in Table 10.2-1. The reports will be provided as required by the study plan, IRB policies, or local regulations, whichever is more stringent.

Table 10.2-1. Early Termination or Suspension Reports

Report	To	Timeframe to submit report (upon awareness)
IRB initiated suspension or early termination	Sponsor Patient	Within 5 working days
Sponsor initiated suspension or early termination	IRB Patient	Within 5 working days

The sponsor is responsible for reporting early termination or suspension of the study to reviewing IRB(s) and principal investigator(s) as required according to applicable regulations/standards.

11.0 Statistical Considerations

11.1 Sample Size

The expected rates of adjunctive therapy for the Enforcer balloon and conventional angioplasty groups were assumed to be 5% and 15%, respectively. A sample size of at least 250 total lesions (125 lesions per group) is required to detect a 10% difference in the rate of adjunctive therapy with a power of 80% and a type I error of 0.05. Prior experience suggests that 40% of patients, on average, would also have a second lesion treated. Therefore the study will enroll approximately 200 patients (approximately 100 patients per group) and enrollment will continue until at least 250 lesions are treated. Procedural outcomes are unlikely to depend on the connectivity between lesions within an AV dialysis access circuit or the patient-level factors which affect longer-term outcomes, and therefore lesions were assumed to be independent for the purposes of the sample size calculation.

Up to 10 clinical sites will be included in the study, and the maximum enrollment per clinical site will be no more than 80 patients or 40% of the total enrollment. There is no minimum enrollment threshold. Patients that withdraw from the study will not be replaced.

11.2 Randomization

Once patient eligibility is confirmed, patients will be randomized into either the Enforcer balloon or conventional angioplasty group prior to treatment in a 1:1 ratio at each study site. Randomization will be first stratified by the number of lesions requiring treatment (single lesion or two lesions) and type of AV access circuit (fistula or graft). Using restricted randomization maximizes the balance of treatment allocations within stratum and vice versa. Randomization codes will be maintained by the Sponsor.

11.3 Analyses

11.3.1 Primary endpoint analysis

The study is intended to compare the necessity of adjunctive therapies for lesions treated with the study device (Enforcer balloon) compared to those treated with the control device (conventional angioplasty balloon inflated to standard pressures). The null (H_0) and alternative (H_A) hypotheses are expressed as follows:

H_0: $AT_{EB} \geq AT_{CA}$
H_A: $AT_{EB} < AT_{CA}$

where AT_{EB} is the rate of adjunctive therapies in the Enforcer balloon group and AT_{CA} is the rate of adjunctive therapies in the conventional angioplasty balloon group.

The rates of adjunctive therapies will be compared between the two treatment groups with a one-sided Z-test. A p-value < .05 will be used to claim statistical significance. If the number of patients within each strata are sufficiently large, the association of stratification factors and treatment will be assessed. Crude and adjusted, if applied, differences in rate of adjunctive therapies between the two treatment groups and 95% confidence intervals will be reported.

11.3.2 Analysis of secondary endpoints

Differences in pain, procedural costs, procedure times, and maximum balloon pressure will be assessed overall by one-sided t-tests, with Enforcer balloon having favorable outcomes. In addition, regression models will be used to incorporate the stratification factors as covariates and reported if found to be significant. If the parametric assumptions are not met, nonparametric methods will be used. The safety claim will be evaluated with a Z-statistic, with a non-inferiority of Enforcer balloon at a margin of 10%. The observed non-inferiority margin will also be presented.

Adjustments for multiplicity will be made using the Holm procedure to control the family-wise error rate to 0.05 across the family of secondary endpoints.

11.3.3 Analysis of additional measures

The same analysis strategies will be applied to the additional measures. For continuous measures, the difference between the two treatment groups will be assessed by t-test statistics. The impact of the two stratification variables on the outcomes between the two groups will also be explored, and reported if the test suggests a difference. If the parametric assumptions are not met, nonparametric methods will be used. Survival analysis techniques such as Kaplan-Meier or Cox Proportional Hazards will be incorporated if censoring of data occurs.

Key components of the additional measures may also be compared, including specific adverse events associated with the procedure, such as vessel rupture or tear.

11.4 Missing Data

For the primary endpoint, minimal or no missing data is expected. Missing primary outcome will be assumed missing at random and excluded for analyses. However, if more than 5% of primary endpoint is missing, multiple imputation technique will be applied followed by sensitivity analyses. All the other measurements will be analyzed accordingly with all available data using a complete case approach.

11.5 Site-level Poolability

This is a multi-center study with up to 10 clinical sites. It is not intended to incorporate study sites into primary endpoint analyses. However, the primary endpoint will be examined across sites and reported if necessary.

12.0 Deviations from Study Plan

Except under emergency situations when necessary to preserve the rights, safety, or well-being of study patients, principal investigators are not allowed to deviate from this study plan without documented prior approval by:

- the sponsor; and
- the IRB

Clinical study noncompliances (i.e., deviations from the study plan, investigator agreement, IRB policy, and/or any applicable regulations/standards) will be documented, along with an explanation and corrective and preventive actions, and reported to the sponsor.

The principal investigator-required notifications/reports are described in Table 12.0-1. The reports will be provided as required by the study plan, IRB policies, or local regulations, whichever is more stringent.

Table 12.0-1. Clinical Study Noncompliance Reports

Report	To	Timeframe to submit report (upon awareness)
Deviation to protect the life or physical well-being of a patient in an emergency	Sponsor IRB	As soon as possible, but no later than 5 working days
Deviation that affects the scientific soundness of the clinical study	Sponsor IRB	Within 5 working days
All clinical study noncompliances	Sponsor IRB, if required per local policy	15 working days

The sponsor is responsible for reporting clinical study noncompliances to the reviewing IRB(s) and investigator(s) as required according to applicable regulations/standards.
In accordance with applicable regulations/standards, the sponsor will review all clinical study noncompliances and take suitable action(s) to secure compliance. If appropriate, based on the number and nature of noncompliances, actions may include discontinuation of device shipment and/or termination of a principal investigator's participation in this clinical study.

13.0 Data Collection and Management

Patient data will be documented and recorded by trained personnel at the clinical site onto eCRFs through an EDC system. This is a secure, validated, web-based system, allowing those with permission to access data from any location at any time. Source data must be retained for all data entered into the EDC system. The patient-reported pain assessment and the physician assessment of the quality and performance of the study product may be directly entered into the EDC system.

Clinical site personnel are required to undergo training and will have unique login names and passwords in order to enter patient data. In accordance with 21 CFR Part 11, the EDC system creates a secure, computer-generated, time stamped audit trail to record the date and time of operator entries and actions that create, modify, or delete electronic records. Principal investigators will review and electronically sign the eCRFs to confirm that the data recorded are accurate and complete.

Principal investigators will provide all applicable clinical data and documentation to the sponsor in a timely manner. All clinical study documents (including patient data) must be retained as required by the applicable regulations/standards. The principal investigator or

clinical site personnel are requested to contact the sponsor before removing any documents pertaining to the clinical study. The sponsor is responsible for database management, data verification, data archiving, and data retention.

As needed to assist the sponsor in its research (e.g., during evaluation of an adverse event), data will be accessible to the sponsor, the participating principal investigators, the manufacturer, and companies or individuals the sponsor authorizes.

14.0 Monitoring

The conduct of the clinical study will be supervised through a process of centralized, remote, and on-site monitoring.

The sponsor will perform centralized monitoring (i.e., data review) throughout the study for adverse events, unexpected results, and for data completeness, consistency, and clarity. A formal query process in the EDC system will be utilized to resolve data discrepancies. Queries may arise from automated processes or from manual review of eCRFs, procedural reports, imaging data, or correspondence received. Principal investigators will ensure timely resolution of queries.

On-site monitoring will be implemented as necessary throughout the course of the study to ensure the principal investigators are fulfilling the obligations set forth in the study plan, agreement(s), IRB policies, and applicable regulations/standards. Source data verification will be performed during on-site visits. If allowed per site policy, some source data verification may be done remotely, according to the monitoring plan. The principal investigator and clinical site will provide direct access to source data/documents for study-related monitoring, audits, IRB review and regulatory inspection. Standard practices for monitoring the study are summarized in Appendix C.

15.0 Clinical Study Administration

15.1 Approvals

The principal investigator is responsible for obtaining approval of this clinical study (including the study plan, informed consent form, and all patient materials) from the relevant IRB at their associated clinical site. The clinical study will not begin at a particular clinical site until a favorable opinion of the IRB has been obtained. The study plan and other clinical study documents may be revised by the sponsor, as appropriate,

based on new or changes to important information. A summary of the study plan revision history will be documented by the sponsor. Changes or modifications to the study plan, informed consent form, or patient materials may not be initiated without IRB approval. The principal investigator is responsible for keeping their IRB informed as to the progress of the study and complying with requirements imposed by their IRB. Furthermore, the sponsor and the principal investigator will ensure that local regulations concerning data protection are followed.

15.2 Clinical Study Reporting

Principal investigators will provide the notifications/reports described in Table 15.2-1. The reports will be provided as required by IRB policies.

Table 15.2-1. Clinical Study Reports

Report	To
Withdrawal of IRB approval	Sponsor
Progress report	IRB
Final report	IRB

The sponsor is responsible for providing progress reports and final reports, notification of study completion or termination, and reporting significant findings to the reviewing IRB(s) and principal investigator(s) as required according to applicable regulations/standards.

15.3 Contact information

Refer to Appendix A for a list of the sponsor, monitor, and manufacturer. Contact information and qualifications for the clinical site(s), principal investigator(s), or other institutions involved, will be maintained by the sponsor. The sponsor will also maintain contact information for each reviewing IRB.

15.4 Insurance

Insurance for the study will be obtained by the sponsor prior to patient enrollment.

16.0 Publication Policy

This clinical study will be registered on www.ClinicalTrials.gov and the intent is to make study results public. Publication policy, rights, and obligations for this study will be

negotiated, detailed, and defined in the clinical study's contractual documents with the clinical site and principal investigator.

17.0 References

1. Rajan DK. Balloon angioplasty for low-flow access. *J Vasc Access*. 2015;16 Suppl 9:S66-7.
2. Holden A. Advance 35 Scoring PTA Balloon Dilatation Catheter: 6-Month Results. Presented at: Charing Cross International Symposium; April 2016; Olympia, London, UK.
3. National Kidney Foundation. NKF-K/DOQI Clinical practice guidelines and clinical practice recommendations for 2006 updates: hemodialysis adequacy, peritoneal dialysis adequacy and vascular access. *Am J Kidney Dis* 2006;48(suppl.1):S188–91

APPENDIX A: Contact Information

Global Sponsor and Monitor

Cook Research Incorporated
1 Geddes Way
West Lafayette, IN 47906
USA

Contact:	Jennifer L. Kerr
	President
Telephone:	765.463.7537
Fax:	765.497.0641
E-mail:	Jennifer.Kerr@CookMedical.com

Manufacturer

Cook Incorporated
750 Daniels Way
Bloomington, IN 47404 U.S.A.

APPENDIX B: Schedule of Events

	Pre-procedure	Procedure	Follow-up
			90 days
Informed consent	X		
Demographics	X		
Medical history	X		
Physical exam	X		
Baseline angiography	X		
Randomization		X	
Angioplasty		X	
Completion angiography[a]		X	
Patient-reported Pain Assessment		X	
Chart Review			X
Adverse events		X	X[b]

[a] Completion angiography should be performed after treatment with the Enforcer or conventional angioplasty balloon. If an adjunctive procedure is performed, an additional angiography should be performed after completion of that procedure.

[b] Events with an onset date after 90 days post-procedure will not be collected.

APPENDIX C: Standard Practices for Monitoring

1.0 Selection of the monitor

Designated by the sponsor to oversee the clinical study, the monitor may be an employee of Cook, an employee of a Contract Research Organization (CRO), or an independent contractor or consultant. The monitor will be qualified by training and experience and will be familiar with the clinical study product(s), study plan, and applicable regulations/standards.

2.0 General duties of the monitor

Clinical sites will be monitored throughout the clinical study to verify:

- The protection of the rights, safety, and welfare of patients;
- The clinical study is being conducted in accordance with the study plan, agreement(s), IRB policies, and applicable regulations/standards;
- The proper use of the clinical study product;
- Adverse events and clinical study noncompliances are reported; and
- The quality and integrity of the clinical study data.

2.1 Initiating the study

Prior to enrolling a patient, the monitor and/or sponsor representative will participate in a site initiation visit with each clinical site.

At a minimum, the following will be addressed with the principal investigator and appropriate clinical site personnel:

- Training on responsibilities and requirements per the study plan, agreement(s), and applicable regulations/standards; and
- The IRB approval letter and approved informed consent are on file prior to initiation of the clinical study.

2.2 Periodic visits

During the course of the study, the monitor may visit the clinical site to ensure that the obligations set forth in the study plan, agreement(s), IRB policies, and applicable regulations/standards are fulfilled. The frequency of site visits may vary and the following activities will be performed as needed during the course of the study:

- Perform source data verification per the monitoring plan
    - Ensure the reviewed information recorded in the eCRFs is complete, accurate, and legible.
    - Review patient charts for adverse events and ensure that events are appropriately reported.
    - Ensure the reasons for patient(s) failing to complete the study are documented.
- Review Investigator File (e.g., essential documents)
    - Verify that there is a signed/dated informed consent document for each patient enrolled to date and confirm that the correct version of the informed consent was signed and dated prior to performing any study-related procedures.
    - Ensure applicable version of the study plan and agreements are being followed and any changes to the study plan, informed consent form have been approved.
    - Ensure accurate, complete, and timely reports have been made to the sponsor and IRBs if applicable.
    - Ensure the appropriate training records are on file if the Signature and Delegation of Responsibilities Log at the clinical site has been updated.

2.3 Close-out visits

Close-out visits may be conducted via an on-site or telephone call to ensure, at minimum:

- Reviewed data are accurate and complete or a justification has been provided for any missing data
- All previously identified follow-up items and clinical study non-compliances have been reported and resolved, if applicable
- All essential documents have been filed at the clinical site
- The principal investigator understands their obligations regarding documentation and retention requirements.

3.0 Records and reports of the monitor

Following each site initiation visit, periodic visit, and close-out visit, a follow-up letter to summarize the visit will be sent to the clinical site.

APPENDIX D Definitions

Adjunctive Therapy: Additional treatment necessary for achievement of clinical success immediately following treatment with the study device (Enforcer balloon) or control device (conventional balloon angioplasty). Adjunctive therapies may include high-pressure balloon angioplasty, cutting balloon angioplasty, stents or stent graft.

Adverse Event: Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in patients, users, or other persons, whether or not related to the investigational medical device. Refer to Section 9.6: Adverse Events for a list of reportable events.

Anatomic Success: Residual stenosis less than 30% within the treated lesion following the study procedure (including adjunctive therapy).

Arteriovenous (AV) Hemodialysis Access Circuit (also Access Circuit, Dialysis Access Circuit):

- AV Fistula - The vascular conduit beginning from the arterial inflow (2 cm upstream from the AV anastomosis) and ending at the confluence of the cephalic and axillary veins.
- Graft – The vascular conduit beginning from the arterial inflow (2 cm upstream from the artery-graft anastomosis) and ending at the confluence of the cephalic and axillary veins.

AV Hemodialysis Access Circuit, Mature: Native fistula has been successfully used for at least one hemodialysis treatment. Grafts included in the study will have also been successfully used for at least one hemodialysis treatment.

Clinical or physiological abnormalities which indicate dialysis access dysfunction: Abnormalities may include the following:

- Decreased access blood flow (e.g., <600ml/min, decrease in flow)
- Elevated venous pressure
- Decreased dialysis dose (Kt/V)
- Abnormal physical exam

Clinical Success: Resumption of normal dialysis for at least one session.

Conventional Angioplasty Balloon: A balloon catheter having a rated burst pressure less than 25 atmospheres.

Device Deficiency: Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance.

Device Success: Residual stenosis less than 30% within the treated lesion immediately after angioplasty with the study device (Enforcer or conventional angioplasty balloon).

Dissection: Linear filling defect due to disruption of the intima, staining within the vessel wall.

High-Pressure Angioplasty Balloon: A balloon catheter having a rated burst pressure greater than or equal to 25 atmospheres.

Numeric Rating Scale (NRS) for pain: Assessment of patient-reported pain using a scale from 0 to 10 where 0 indicates no pain and 10 indicates worst possible pain. Patients will be instructed to rate the pain they feel associated with the balloon inflations during the study procedure.

Occlusion: No flow can be identified through the study lesion.

Percent (%) stenosis: Estimated by comparing the closest segment of vessel having the most normal appearance (i.e. the reference vessel).

Primary Patency: Uninterrupted patency of the AV hemodialysis access circuit. Loss of primary patency occurs when a restenosis or occlusion of the AV hemodialysis access circuit results in:

- a reintervention or
- abandonment of the AV dialysis access

Reintervention: Any endovascular or surgical intervention performed in the study-treated AV hemodialysis access circuit.

Rupture: Disruption of the vessel wall allowing marked extravasation of contrast outside the vessel.

Serious Adverse Event: Adverse event that:

a. Led to death,
b. Led to serious deterioration in the health of the patient, that either resulted in:
    i. A life-threatening illness or injury, or
    ii. A permanent impairment of a body structure or a body function, or
    iii. Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the study plan, without serious deterioration in health, is not considered a serious adverse event.

Thrombosis: Platelet or fibrin deposition within the treated segment successfully treated with thrombolysis or thrombectomy.