Medtronic

Cover page for Statistical Analysis Plan

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Official title of study:	Randomized Study of IN.PACT 014 Paclitaxel-Coated Percutaneous Transluminal Angioplasty Balloon Catheter vs. Optimal Percutaneous Transluminal Angioplasty for the Treatment of Chronic Total Occlusions in the Infrapopliteal Arteries
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Medtronic **Statistical Analysis Plan**	
Clinical Investigation Plan Title	Randomized Study of IN.PACT 014 Paclitaxel-Coated Percutaneous Transluminal Angioplasty Balloon Catheter vs. Optimal Percutaneous Transluminal Angioplasty for the treatment of chronic total occlusions in the infrapopliteal arteries
Clinical Investigation Plan Identifier	APV- IN.PACT BTK OUS
Clinical Investigation Plan Version	7.0
Sponsor/Local Sponsor	Medtronic Peripheral Vascular Health 3850 Brickway Boulevard Santa Rosa, CA 95403 United States Medtronic Bakken Research Center BV Endepolsdomein 5 6229 GW Maastricht The Netherlands

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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Not Applicable, New Document	Pei Li, Principal Statistician
2.0	Update the SAP following the CIP revision 6. Update study sample size update to 50 and change precision of estimate to 0.25 7.9.1 Add subsegmental analyses method for primary endpoint Late Lumen Loss and other Angiographic measurements 7.9.2 Specify that site reported data will be used for clinical success endpoint if core lab data is not available 10.1.1 "All clinical/safety endpoints will have the same denominator at a single time point." Changed to "All clinical/safety endpoints will have the event specific denominator at a single time point." • 10.1.2 Add details for selection of evaluable Angiographic Assessment for 9-month Late Lumen Loss	Pei Li, Principal Statistician
3.0	Update the SAP following the CIP revision 7 and the new SAP template B. • Extend study follow up to 60 months in 5.2.2, 7.9.2 and 10.1.3. • Add wound healing date imputation method in 7.4 • Update language in to reflect ISO 14155 requirement • Delete 10.4.1 reporting precision	Pei Li, Principal Statistician
4.0	Revise the SAP statistical methods for Section 7.9.2 Secondary Objectives to appropriately account for an increase in censored observations with increased follow-up duration extended out to 60 months. Revised methods use time-to-event estimates, such as Kaplan-Meier curves, to estimate study objectives. Impacted study objectives are Major Adverse Events, Mortality, Major Target Limb Amputation, Clinical-Driven Target Lesion Revascularization (CD-TLR), Target Lesion Revascularization (TLR), Clinical-Driven Target Vessel Revascularization (CD-TVR), Target Vessel Revascularization (TVR), and Thrombosis.	Tracy Bergemann, Distinguished Statistician

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse Event
AT	As Treated
BTK	Below-The-Knee
CD	Clinically Driven
CEC	Clinical Events Committee
CIP	Clinical Investigational Plan
CLI	Critical Limb Ischemia
CRF	Case Report Form
CSR	Clinical Study Report
CTO	Chronic Total Occlusion
DCB	Drug Coated Balloon
DS	Diameter Stenosis
DMC	Data Monitoring Committee
DUS	Duplex Ultrasound
ITT	Intention-to-Treat
LLL	Late Lumen Loss
MAE	Major Adverse Event
MD	Mechanically Driven
PAD	Peripheral Artery Disease
PTA	Percutaneous Transluminal Angioplasty
QVA	Quantitative Vascular Analysis
RBP	Rated Burst Pressure
RVD	Reference Vessel Diameter
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
TL	Target Lesion
TLR	Target Lesion Revascularization
TV	Target Vessel
TVR	Target Vessel Revascularization
USADE	Unanticipated Serious Adverse Device Effect
WIfI	Wound Ischemia and foot Infection
IQR	Interquartile Range

3. Introduction

This document outlines the detailed statistical methods to be implemented for the data collected within the scope of the Medtronic IN.PACT BTK Study. The purpose of this plan is to provide a framework within which answers to the study objectives can be achieved in a statistically rigorous fashion, without bias or analytical deficiencies. Specifically, the Plan has the following purpose: To prospectively (a priori) outline the types of analyses and presentations of data that will form the basis for conclusions to be reached that will answer the clinical evaluation objectives outlined in the protocol, and to explain in detail how the data will be handled and analyzed, adhering to commonly accepted standards and practices of biostatistical analysis in the medical device industry. Results obtained from the analyses outlined in this document will be the basis of the Clinical Study Report (CSR) for the overall Clinical Investigational Plan (CIP).

4. Study Objectives

4.1 Primary Objective

To assess the effectiveness of the IN.PACT 014 by comparing the Late Lumen Loss (LLL) of the investigational product vs optimal (conventional) Percutaneous Transluminal Angioplasty (PTA).

4.2 Secondary Objective(s)

To assess the safety of the IN.PACT 014 by comparing pre-specified safety parameters of the investigational product vs optimal (conventional) PTA. Other pre-specified parameters assessing efficacy and safety and clinical utility measures will be evaluated and rates will be compared for the IN.PACT 014 vs optimal PTA.

5. Investigation Plan

This is a prospective, multi-center, randomized (1:1) study to evaluate the effectiveness and safety of the IN.PACT 014 in the treatment of Chronic Total Occlusion (CTOs) in the infrapopliteal arteries. Enrollment per site should be limited to around 30% of the total enrollment.

The study will enroll a minimum of 50 subjects that will be randomized to the investigational product (IN.PACT 014) or optimal PTA balloon. Randomization will happen after screening of the subject, to assess whether the subject meets all the inclusion criteria and does not meet any of the exclusion criteria specified in the protocol; this includes meeting the criteria for successful Optimal PTA in the target lesion(s).

Patient randomization will be determined centrally by means of a web-based system.

5.1 Selection of Subjects

5.1.1 Study Population

The study population will be comprised of patients with symptomatic chronic Critical Limb Ischemia

(CLI) who are candidates for percutaneous endovascular intervention and who meet the Inclusion/Exclusion criteria.

Subjects enrolled in this study will be comprised of adult male and female subjects derived from:

- Individuals referred to a non-invasive vascular laboratory for assessment of the peripheral arterial disease (PAD)
- Angiography suites
- Clinical practice: subjects presenting to the investigator's practice with chronic symptoms in the lower extremity(s), PAD are potential study candidates

The study will enroll a minimum of 50 subjects at approximately ten (10) European sites.

5.1.2 Subject Enrollment

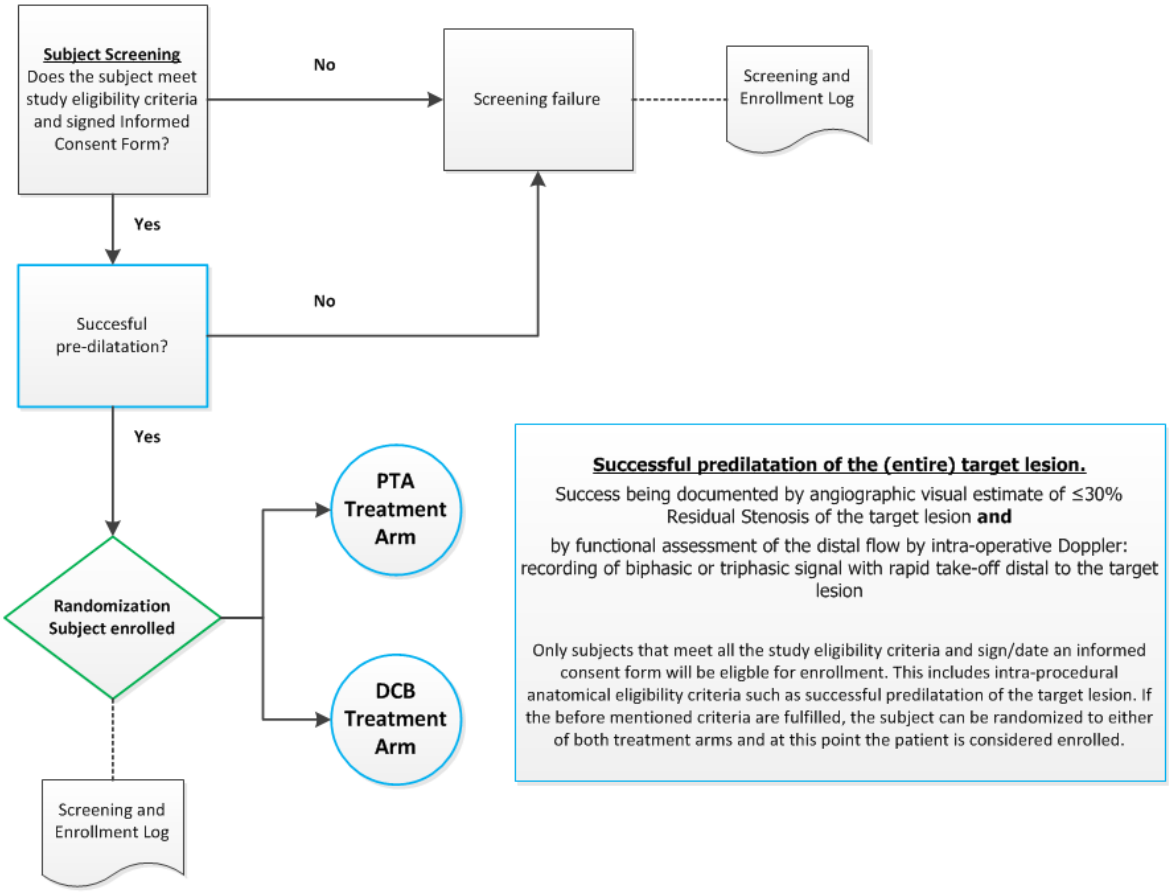
Only subjects that meet all the study eligibility criteria and sign and date an informed consent form will be eligible for enrollment. This includes intra-procedural anatomical eligibility criteria such as successful pre-dilatation of the target lesion(s). If the aforementioned criteria are fulfilled, the subject can be randomized to one of the treatment arms and at this point the subject is considered enrolled.

The point of enrollment is only considered after successful pre-dilatation because until then only standard of care procedures are followed. Enrolled subjects will be documented on the Screening and Enrollment log. Subjects who are enrolled, but in whom the device does not cross the (target) lesion will be followed through the 1-month follow-up only.

Subjects who do not qualify for enrollment will be documented as ineligible on the Screening and Enrollment log.

From the subjects enrolled in the IN.PACT BTK Study, as shown in **Figure 1**, all randomized subjects will be included in this analysis.

Figure 1. Subject Enrollment Flow



5.2 Endpoints

5.2.1 Primary Endpoint

The primary effectiveness endpoint will be Late Lumen Loss (LLL) at 9 months post procedure for the IN.PACT 014 Investigational device vs optimal PTA. LLL will be assessed by means of Quantitative Vascular Angiography (QVA) by an independent angiographic core lab at 9 months post procedure or at the time of TLR (prior to any intervention on the target lesion), whichever occurs first.

Restenosis of the target lesion remains an important problem in the treatment of occlusive lesions in below the knee arteries. Neointimal proliferation is a major culprit leading to a decrease in the arterial luminal diameter and eventually (re)stenosis. As it is expected that paclitaxel will reduce this neointimal proliferation, LLL has been selected as primary endpoint.

5.2.2 Secondary Endpoints

- Composite Safety Endpoint: A composite of freedom from device- and procedure-related mortality within 30 days, freedom from major target limb amputation and freedom from clinically-driven TLR within 9 months post-index procedure
- Major Adverse Event (MAE) rate, defined as a composite of all-cause mortality, target limb major amputation and clinically-driven TLR through 3, 6, 9, 12, 24, 36, 48 and 60 months
- Functional flow assessment at 3, 6, 9, 12, 24 and 36 months, defined as absence of target lesion occlusion (no flow) assessed by duplex ultrasound (DUS)
- Death of any cause and cardiovascular related deaths through 3, 6, 9, 12, 24, 36, 48 and 60 months
- Rate of major target limb amputation through 1, 3, 6, 9, 12, 24, 36, 48 and 60 months
- Rate of CD-TLR through 3, 6, 9, 12, 24, 36, 48 and 60 months
- Rate of Mechanically Driven TLR through 37 days
- Rate of TLR through 3, 6, 9, 12, 24, 36, 48 and 60 months
- Rate of CD-TVR through 3, 6, 9, 12, 24, 36, 48 and 60 months
- Rate of TVR through 3, 6, 9, 12, 24, 36, 48 and 60 months
- Status of wound healing (completely healed - improvement – unchanged – worsened) at 30 days, 3, 6, 9, 12, 24 and 36 months
- Rate of thrombosis at the target lesion(s) through 30 days, 3, 6, 9, 12, 24, 36, 48 and 60 months
- Device success (for investigational device only)

  Device success is defined as successful drug delivery, balloon inflation, deflation and retrieval of the intact study device without burst below the rated burst pressure (RBP)
- Clinical success

  Clinical success is defined as residual stenosis of ≤ 30% without procedural complications (death, major target limb amputation, thrombosis of the target lesion, or TVR) prior to discharge

6. Determination of Sample Size

Limited studies in BTK reported LLL data. LLL results are displayed in the **Table 1** below for four previous studies which reported LLL either at 6 or 12 months. Based on these previous studies, standard deviation of LLL at 9 months is estimated to be ~0.60 mm for DCB and PTA group. Randomization will be done in a 1:1 fashion.

Assuming 15% attrition due to death and lost- to-follow up, and multiple lesions (~1.1 on average) per subject being allowed in the study, it is expected to have 21 subjects with 23 evaluable LLL measurements at 9 months for each arm. The precision or margin of error, of the estimated LLL can be assessed by calculating the distance from the upper limit of the 95% confidence interval to the mean. With 23 lesions

in each arm, the precision (half of the width of the confidence interval) is calculated to be 0.25 mm. The precision of the LLL difference between the two arms is calculated to be 0.35 mm.

Table 1. LLL results for four previous studies

Study Name	Endpoint Time	Drug Coated Balloon	Percutaneous Transluminal Angioplasty	Drug Eluting Stent
IDEAS[1]	6 months	1.15±0.3 mm	Not applicable	1.35±0.2 mm
DEBELLUM[2]	12 months	0.66±0.9 mm	1.69±0.5 mm	Not applicable
BIOLUX PII[3]	6 months	0.56±0.65 mm	0.54±0.66 mm	Not applicable
IN.PACT DEEP[4]	12 months	0.605±0.775 mm	0.616±0.781 mm	Not applicable

No formal hypothesis test is specified for this study. A sample of 50 subjects will provide good precision to quantify the target parameter of LLL. Primary analysis will be performed when all subjects have completed 9-month visits. The study may be extended to a larger clinical study upon appropriate ethical and clinical justifications, to be included in the premarket clinical evaluation cohort in US. Statistical justifications including type I error control and power will be provided to retain a high level of scientific rigor. Additionally, an independent Data Monitoring Committee (DMC) will be appointed to closely monitor the study progress and make recommendations based on study outcomes.

7. Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

The number of subjects who are screened, randomized and received therapy, and who have a scheduled follow-up visit will be summarized at each scheduled visit.

7.1.2 Clinical Investigation Plan (CIP) Deviations

Protocol deviations will be reported descriptively by counts of type and listing by site.

7.1.3 Analysis Sets

Intention-to-treat (ITT): The ITT analysis cohort will include all randomized subjects in the groups to which they are randomized regardless of the treatment received and will serve as the primary analysis cohort for each objective unless otherwise specified.

As Treated (AT): The AT cohort includes randomized subjects but analyzes subjects using the treatment they actually received. The AT cohort excludes subjects that were randomized but never received treatment. Additionally, for example, if a subject were randomized to the DCB group, but received the PTA treatment the subject would be included in the PTA group for analysis purposes.

The definition of the analysis sets is based on intention rationale, but the actual analysis will be based on the available data in each analysis set.

Primary analysis will be performed based on ITT analysis set.

7.2 General Methodology

Descriptive statistics (frequency and percentage for categorical variables and number of observations, mean, standard deviation, median, IQR, minimum, and maximum for continuous variables) will be reported. Subject data listings and tabular and graphical presentations of results will be provided. For primary and secondary endpoints, 95% confidence intervals will be calculated.

Intention-to-treat analysis will serve as the primary analysis for all study endpoints. As treated analysis may be performed as sensitivity analysis if patient crossover occurs.

Statistical analyses will be conducted in SAS® version 9.4 or above (SAS Institute, Cary, N.C.) or another validated statistical software package.

Schedule of Events

The schedule of study procedure and assessments is listed below in **Table 2**.

Table 2: Schedule of study procedures and assessments

	Screening	Procedure	Discharge	30 days (± 7 days)	3 months (±15 days)	6 months (±30 days)	9 months (±60 days)	12 months (±30 days)	24 months (±30 days)	36 months (±30 days)	48 months (±30 days)	60 months (±30 days)	Unscheduled	Upon Early Termination
	Visits										Phone Calls		Visit	Phone Calls
Inclusion/Exclusion and consent	X										X[6]			
Physical Exam	X		X	X	X	X	X	X	X	X			X	
Medical history and demographics	X													
DUS		X[3]	X[4]	X	X	X	X	X	X	X			X[5]	
ANGIOGRAPHY		X					X						X[5]	
Rutherford Classification	X			X	X	X	X	X	X	X			X	
Medications	X	X	X	X	X	X	X	X	X	X			X	
WIfI assessment	X		X	X	X	X	X	X	X	X			X	
Wound care / Assessment[1]	X[2]		X	X	X	X	X	X	X	X			X	
EQ-5D	X		X	X	X	X	X	X	X	X			X	
Adverse Events Assessment		X	X	X	X	X	X	X	X	X	X	X	X	
Vital Status														X[7]

1. For as long as applicable
2. Includes WIfI classification at baseline visit
3. Duplex Ultrasound for Reference Vessel Diameter measurements and Procedural Duplex Ultrasound Doppler Examination to determine successful pre-dilatation
4. DUS assessment if available, should be prior to discharge,.
5. In case an angiography / DUS of the study limb is done during an unscheduled visit it has to be provided to sponsor
6.
   - Ensure subject is reconsented prior to conducting any study specific assessments after 36 months.
   - In case the subject exited the study at 36 months post procedure or before, ensure that the subject is picked up again in the study through reconsenting, prior to conducting any study-specific assessments after 36 months, if allowed by local regulations.
7. Collection of information about (vital) health status for exited subjects, upon subject's consent until 60 months after index procedure

Study day will be calculated from the date of index procedure, i.e. Day 0. Study day of an event will be calculated as date of the event minus date of index procedure. Day 1 is the day immediately after the index treatment. Study day of an event which occurs prior to Day 0 will be presented as a negative number, if any, and such events will NOT be included in the post index procedure analysis.

General Analysis Definitions

Assessments will be presented chronologically by study day, which is defined in the following:

Study day = date of assessment – date of index procedure

Index procedure day = Day 0. Events occurring on the day of the index procedure will be considered on Day 0.

Events occurring on or prior the discharge day and on or after index procedure day will be considered as in-hospital events.

Duration of Study Follow-up

For subjects that consented to the study extension, the duration of study follow-up is calculated as follows. If a subject is not expired, then duration of follow-up will be calculated from the last date of

follow-up visit or the final assessment, whichever is later. If a subject is expired, then the duration of follow-up will be calculated using the date of death. If a subject exits the study prior to completing study follow-up, the duration of follow-up will be calculated using the date of exit. Data reported after the date of exit, will be excluded from reporting. For subjects that did not reconsent to the study extension and did not consent to vital status collection, the duration of study of follow-up is calculated in the same way as above.

For subjects that did not reconsent to the study extension but did consent to vital status collection, the duration of study of follow-up is calculated as follows. If a subject has not expired prior to their 36 month follow-up visit, then duration of follow-up will be calculated from the last date of follow-up visit or the final assessment, whichever is later. If a subject has expired prior to their 36 month follow-up visit, then the duration of follow-up will be calculated using the date of death. If a subject exits the study prior to completing 36 month follow-up visit, the duration of follow-up will be calculated using the date of exit. Data reported after the date of exit will be excluded from reporting, with the exception of vital status.

For any survival analysis with death as an endpoint, the follow-up time is calculated using date of death, date of exit, or date of vital status assessment where the subject status is alive, whichever is later.

7.3 Center Pooling

The study will enroll at a minimum 50 subjects at approximately ten (10) European sites. Study data from the sites will be pooled for analysis. There is no formal hypothesis testing for poolability due to the small sample size of the study. Primary endpoint (LLL at 9 months) results for each site may be presented by treatment if needed.

7.4 Handling of Missing, Unused, and Spurious Data and Dropouts

In general, analysis will be based on all the data reported in the CRF. Imputation of missing data will not be performed for all analyses. Subjects who dropped out will be censored at date of last follow-up contact. The reason for drop out will be summarized in a listing. For study endpoints, missing data will be listed with patient numbers for review.

Incomplete date

Unless otherwise specified, the following rules shall be applied in raw data at the database level:

Imputed dates will be applicable to AE start date and any other date that could be used to derive the last date except the exit date due to the reason of death.

If a date needed for calculation is an incomplete date (e.g. **111956 or ****1956), it will be completed as follows:

1. For incomplete event dates, ‘01’ or ‘0101’ will be entered, respectively (worst case)
2. If an imputed event date is before date of index procedure, the date of event will be set equal to the date of index procedure

3. For all other incomplete dates, '15' or '0107' will be entered, respectively (less far from correct date). In addition, if the missing month is known to be between January and July, or between July and December, the mid-month between last known month and December may be used.
4. For wound healing date, the worst-case scenario will be used which is the last day of the month in case of a missing day, or last day of the year in case of a missing month.

7.5 Adjustments for Multiple Comparisons

This is not a hypothesis driven study and hence multiplicity adjustment is NOT applicable.

7.6 Demographic and Other Baseline Characteristics

All demographic, medical history and clinically relevant baseline variables will be summarized and tabulated. Descriptive statistics will be presented as follows:

- Categorical variables, including binary variables, will be reported by giving the number and percentage of patients in each category.
- Continuous variable will be reported by presenting the number of observations, mean, standard deviation, median, IQR, minimum, and maximum of each variable.

7.7 Treatment Characteristics

Procedural characteristics such as days of hospitalization, number of devices used, device success, provisional stenting use and etc., will be summarized by treatment arms (i.e. frequency and percentages for categorical variables, and number of observations available, mean, standard deviation, median, IQR, minimum, and maximum for continuous variables).

7.8 Interim Analyses

Interim analyses were pre-specified to be conducted and reviewed by an unblinded predesignated group when 15, 30, 45 and/or when all subjects enrolled are randomized and followed up for 9 months. A decision to stop, continue or extend the study can be made after each interim analysis has been reviewed. As the study has no formal hypothesis testing at each of the interim analyses, no multiplicity adjustment is needed. Due to the timing of analysis during the execution of the study and revision in the total sample size from 60 subjects down to 50 subjects in CIP v5, interim analysis was conducted only for 31 subjects enrolled, but no analysis was conducted for 15 or 45 subjects. After primary endpoint analysis, additional analysis may be performed upon the discretion of the sponsor.

7.9 Evaluation of Objectives

7.9.1 Primary objective

Objective

To assess the effectiveness of the IN.PACT 014 by comparing the Late Lumen Loss (LLL) of the investigational product vs optimal (conventional) PTA.

Endpoint

The primary effectiveness endpoint will be Late Lumen Loss (LLL) at 9 months post procedure for the IN.PACT 014 Investigational device vs optimal PTA. Late lumen loss is assessed by comparing the minimal lumen diameter (MLD) within the treated segment immediately after the procedure with the MLD within the treated segment 9 months later at the scheduled follow-up visit, or sooner in the event of recurrent symptoms due to restenosis. The MLD will be assessed by means of Quantitative Vascular Angiography (QVA) by an independent angiographic core lab immediate post-procedure, and at 9 months post procedure or at the time of TLR. The LLL will be summarized at lesion level.

$$Late\ Lumen\ Loss\ (LLL) = MLD_{Post\ Procedure} - MLD_{9\ mo\ or\ early\ TLR}$$

Analysis Method

Primary analysis will be performed by ITT principle, which constitutes all evaluable angiographic images at 9 months post procedure or at the time of revascularization, whichever comes first. Summary statistics (mean, standard deviation, median, IQR, minimum, maximum) for LLL will be calculated for each randomized group. The difference between the two groups and the 95% confidence interval will be presented.

As Treated (AT) analysis may be used as sensitivity analysis if patient crossover occurs.

Due the recognized limitations of using a single MLD within a treated segment as a measure for angiographic restenosis due to axial relocation of the MLD, additional exploratory analyses that measure the totality of vessel narrowing within the treated segment will be performed. These additional analyses identify 10 equal sub-segments within each treated lesion; subsegmental measures include determining the mean and minimal diameters within each subsegment matched with the baseline, post-procedural, and follow-up angiograms. These measures provide subsegmental mean and minimal acute lumen gain immediately after the procedure, mean and minimal LLL at follow-up, mean and minimal net lumen gain from baseline to follow-up, mean and minimal loss index, defined as the ratio of LLL divided by acute gain. In aggregate, these measures will provide a more detailed insight into the totality of lumen re-narrowing between active and control treatments

7.9.2 Secondary Objectives

- **Composite Safety Endpoint**

Endpoint

The composite safety endpoint will be a composite of freedom from device- and procedure-related mortality within 30 days, freedom from major target limb amputation and freedom from clinically-driven TLR within 9 months post-index procedure.

Analysis Method

The success rate of safety endpoint will be defined as the number of subjects without any device and procedure-related death within 30 days, major target limb amputation and CD-TLR within 9 months post-index procedure adjudicated by CEC divided by number of evaluable subjects at 9 months. Percentage and 95% confidence interval will be calculated for the safety endpoint success rate for each randomization arm respectively.

- **MAE Endpoint**

Endpoint

Major Adverse Event (MAE), defined as a composite of all-cause mortality, target limb major amputation and clinically-driven TLR through 3, 6, 9, 12, 24 , 36, 48 and 60 months.

Analysis Method

The MAE rate through 60 months will be calculated using a Kaplan-Meier curve for each randomization arm. Analyses will include event-free survival probabilities and 95% confidence interval bands through the 60-month visit. The confidence intervals will be calculated using a typical transformation of the survival function: log(S(t)). Subjects who experience death, target limb major amputation or CD-TLR post-index procedure as adjudicated by CEC will be counted as an event. Subjects not completing the study will be censored after their last available visit. Results from the Kaplan-Meier estimates will be reported at 3, 6, 9, 12, 24, 36, 48 and 60 months for each randomization arm respectively.

- **Functional flow assessment**

Endpoint

Functional flow assessment at 3, 6, 9, 12, 24 and 36 months, defined as absence of target lesion occlusion (no flow) assessed by duplex ultrasound (DUS).

Analysis Method

Summary statistics (frequency percentage etc.) for occlusion rate among lesions with evaluable duplex ultrasound (DUS) data assessed by core lab at each visit will be provided for each arm.

- **Mortality Rate**

Endpoint

Death of any cause through 3, 6, 9, 12, 24, 36, 48 and 60 months.

Analysis Method

Death rate through 60 months will be calculated using a Kaplan-Meier curve for each randomization arm. Analyses will include event-free survival probabilities and 95% confidence interval bands through the 60-month visit. The confidence intervals will be calculated using a typical transformation of the survival function: log(S(t)). Subjects who experience death post-index procedure will be counted as an event. Subjects not completing the study will be censored after their last available visit. Results from the Kaplan-Meier estimates will be reported at 3, 6, 9, 12, 24, 36, 48 and 60 months for each randomization arm respectively.

Endpoint

Cardiovascular related death through 3, 6, 9, 12, 24, 36, 48 and 60 months.

Analysis Method

Cardiovascular related death rate through 60 months will be calculated using a Kaplan-Meier curve for each randomization arm. Analyses will include event-free survival probabilities and 95% confidence interval bands through the 60-month visit. The confidence intervals will be calculated using a typical transformation of the survival function: log(S(t)). Subjects who experience cardiovascular related death as adjudicated by CEC will be counted as an event. Subjects not completing the study will be censored after their last available visit. Results from the Kaplan-Meier estimates will be reported at 3, 6, 9, 12, 24, 36, 48 and 60 months for each randomization arm respectively.

- **Major Target Limb Amputation**

Endpoint

Rate of Major target limb amputation through 30 days, 3, 6, 9, 12, 24, 36, 48 and 60 months.

Analysis Method

Major target limb amputation rate through 60 months will be calculated using a Kaplan-Meier curve for each randomization arm. Analyses will include event-free survival probabilities and 95% confidence interval bands through the 60-month visit. The confidence intervals will be calculated using a typical transformation of the survival function: log(S(t)). Subjects who experience target limb major amputation post-index procedure as adjudicated by CEC will be counted as an event. Subjects not completing the study will be censored after their last available visit. Results from the Kaplan-Meier estimates will be reported at 3, 6, 9, 12, 24, 36, 48 and 60 months for each randomization arm respectively.

A sensitivity analysis shall be performed where a cumulative incidence curve is estimated and death will be accounted for as a competing risk. The cumulative incidence curve will be descriptively compared to 1-S(t) where S(t) is the survival function estimated by the Kaplan-Meier method.

- **Clinical-Driven Target Lesion Revascularization (CD-TLR)**

Endpoint

Rate of CD-TLR through 3, 6, 9, 12, 24, 36, 48 and 60 months.

Analysis Method

Rate of CD-TLR through 60 months will be calculated using a Kaplan-Meier curve for each randomization arm. Analyses will include event-free survival probabilities and 95% confidence interval bands through the 60-month visit. The confidence intervals will be calculated using a typical transformation of the survival function: log(S(t)). Subjects who experience CD-TLR post-index procedure as adjudicated by CEC will be counted as an event. Subjects not completing the study will be censored after their last available visit. Results from the Kaplan-Meier estimates will be reported at 3, 6, 9, 12, 24, 36, 48 and 60 months for each randomization arm respectively.

A sensitivity analysis shall be performed where a cumulative incidence curve is estimated and death will be accounted for as a competing risk. The cumulative incidence curve will be descriptively compared to 1-S(t) where S(t) is the survival function estimated by the Kaplan-Meier method.

- **Mechanically-Driven Target Lesion Revascularization (MD-TLR)**

Endpoint

Rate of MD-TLR through 37 days.

Analysis Method

Rate of MD-TLR rate through 37 days will be calculated as number of subjects undergo MD-TLR within 37 days post-index procedure adjudicated by CEC divided by the number of evaluable subjects at 37 days. Percentage and 95% confidence interval will be presented for each randomization arm respectively.

- **Target Lesion Revascularization (TLR)**

Endpoint

Rate of TLR through 3, 6, 9, 12, 24, 36, 48 and 60 months.

Analysis Method

Rate of TLR through 60 months will be calculated using a Kaplan-Meier curve for each randomization arm. Analyses will include event-free survival probabilities and 95% confidence interval bands through the 60-month visit. The confidence intervals will be calculated using a typical transformation of the survival function: log(S(t)). Subjects who experience TLR post-index procedure as adjudicated by CEC will be counted as an event. Subjects not completing the study will be censored after their last available visit. Results from the Kaplan-Meier estimates will be reported at 3, 6, 9, 12, 24, 36, 48 and 60 months for each randomization arm respectively.

A sensitivity analysis shall be performed where a cumulative incidence curve is estimated and death will be accounted for as a competing risk. The cumulative incidence curve will be descriptively compared to 1-S(t) where S(t) is the survival function estimated by the Kaplan-Meier method.

- **Clinical-Driven Target Vessel Revascularization (CD-TVR)**

Endpoint

Rate of CD-TVR through 3, 6, 9, 12, 24, 36, 48 and 60 months.

Analysis Method

Rate of CD-TVR through 60 months will be calculated using a Kaplan-Meier curve for each randomization arm. Analyses will include event-free survival probabilities and 95% confidence interval bands through the 60-month visit. The confidence intervals will be calculated using a typical transformation of the survival function: log(S(t)). Subjects who experience CD-TVR post-index procedure as adjudicated by CEC will be counted as an event. Subjects not completing the study will be censored after their last available visit. Results from the Kaplan-Meier estimates will be reported at 3, 6, 9, 12, 24, 36, 48 and 60 months for each randomization arm respectively.

A sensitivity analysis shall be performed where a cumulative incidence curve is estimated and death will be accounted for as a competing risk. The cumulative incidence curve will be descriptively compared to 1-S(t) where S(t) is the survival function estimated by the Kaplan-Meier method.

- **Target Vessel Revascularization (TVR)**

Endpoint

Rate of TVR through 3, 6, 9, 12, 24, 36, 48 and 60 months.

Analysis Method

Rate of TVR through 60 months will be calculated using a Kaplan-Meier curve for each randomization arm. Analyses will include event-free survival probabilities and 95% confidence interval bands through the 60-month visit. The confidence intervals will be calculated using a typical transformation of the survival function: log(S(t)). Subjects who experience TVR post-index procedure as adjudicated by CEC will be counted as an event. Subjects not completing the study will be censored after their last available visit. Results from the Kaplan-Meier estimates will be reported at 3, 6, 9, 12, 24, 36, 48 and 60 months for each randomization arm respectively.

A sensitivity analysis shall be performed where a cumulative incidence curve is estimated and death will be accounted for as a competing risk. The cumulative incidence curve will be descriptively compared to 1-S(t) where S(t) is the survival function estimated by the Kaplan-Meier method.

- **Status of Wound Healing**

Endpoint

Status of wound healing at 30-day, 3, 6, 9, 12, 24 and 36 months.

Analysis Method

Wound status will be assessed by visual estimation from the wound care specialist. Wound statuses are classified as:

- Worsened
- Unchanged
- Improved

- Completely healed
- Amputation
- Skin graft

Percentage of wounds in each category will be presented for each treatment arm at 30-day, 3, 6, 9, 12, 24 and 36 months respectively. Number of new wounds will also be reported.

- **Thrombosis**

Endpoint

Thrombosis at the target lesion through 30 days, 3, 6, 9, 12, 24, 36, 48 and 60 months.

Analysis Method

Rate of thrombosis through 60 months will be calculated using a Kaplan-Meier curve for each randomization arm. Analyses will include event-free survival probabilities and 95% confidence interval bands through the 60-month visit. The confidence intervals will be calculated using a typical transformation of the survival function: log(S(t)). Subjects who experience thrombosis at the target lesion post-index procedure as adjudicated by CEC will be counted as an event. Subjects not completing the study will be censored after their last available visit. Results from the Kaplan-Meier estimates will be reported at 3, 6, 9, 12, 24, 36, 48 and 60 months for each randomization arm respectively.

A sensitivity analysis shall be performed where a cumulative incidence curve is estimated and death will be accounted for as a competing risk. The cumulative incidence curve will be descriptively compared to 1-S(t) where S(t) is the survival function estimated by the Kaplan-Meier method.

- **Device Success**

Endpoint

Device success is defined as successful delivery, balloon inflation, deflation and retrieval of the intact study device without burst below the rated burst pressure (RBP).

Analysis Method

Device success rate will be calculated as the number of IN.PACT 014 Investigational devices with successful delivery, balloon inflation, deflation and retrieval of the intact study device without burst below the rated burst pressure (RBP), divided by the total number of IN.PACT 014 Investigational devices assessed in the study.

- **Clinical Success**

Endpoint

Clinical success is defined as residual stenosis of ≤ 30% without procedural complications (death, major target limb amputation, thrombosis of the target lesion, or TVR) prior to discharge.

Analysis Method

Clinical success rate will be calculated as the number of index procedures with residual stenosis of ≤ 30% by core lab (use site reported data if core lab data is not available) for all target lesions and without

procedural complications (death, major target limb amputation, thrombosis of the target lesion, or TVR) prior to discharge as adjudicated by CEC, divided by the number of total index procedures performed.

7.10 Safety Evaluation

All Adverse Events (AEs) will be coded using MedDRA Code. The AEs identified post index procedure through the follow-up will be tabulated by System Organ Classes (SOC) and Preferred Terms (PT). Frequencies and percentages of AEs and SAEs will be presented by treatment arms.

All Adverse Device Effects (ADEs), Serious Adverse Events (SAEs), and Unanticipated Serious Adverse Device Effects (USADEs)) will be reported in a listing.

A summary of all adverse events and adverse device effects, including a discussion of treatment needed, resolution, and relevant principal investigator's judgment concerning the causal relationship with the investigational devices or procedure will be reported in a listing.

All observed device deficiencies will be reported in a listing.

All deaths and reasons for deaths will be reported in a listing.

7.11 Health Outcomes Analyses

No specific health outcome analysis is planned.

7.12 Changes to Planned Analysis

Changes to planned statistical analyses have been determined to be necessary prior to performing the final analyses, are documented in this amended Statistical Analysis Plan and will be approved prior to the analysis. The changes documented in this amended SAP are not included in CIP v7.0. The statistical methods have been revised to appropriately account for an increase in censored observations due to the study CIP revision that has increased the study follow-up duration out to 60 months. Revised methods use time-to-event estimates, such as Kaplan-Meier and cumulative incidence curves, to estimate study objectives. Impacted study objectives are Major Adverse Events, Mortality, Major Target Limb Amputation, Clinical-Driven Target Lesion Revascularization (CD-TLR), Target Lesion Revascularization (TLR), Clinical-Driven Target Vessel Revascularization (CD-TVR), Target Vessel Revascularization (TVR), and Thrombosis.

Any other deviations or changes from the planned analyses deemed necessary due to violation of critical underlying statistical assumptions, data characteristics, or missing data will be clearly described in the clinical study report with justification and rationale.

8. Validation Requirements

All statistical analysis results will be validated. Level I validation will be used for all safety and effectiveness endpoints specified in the clinical investigational plan as well as all analysis datasets. Validation methods for each statistical output will be documented in the validation report.

9. References

1. Siablis D, Kitrou P, Spiliopoulos S et al. Pactitaxel-Coated Balloon Angioplasty Versus Drug-Eluting Stenting for the Treatment of Infrapopliteal Long-Segment Arterial Occlusive Disease. JACC: Cardiovascular Intervention 2014; 7:1048-56.

2. Fanelli F, Cannavale A, Corona M et al. The Treatment of Lower Extremity Disease: The 'DEBELLUM' – Lower limb multilevel treatment with drug eluting balloon – randomized trial: 1-year results. J Cardiovasc Surg 2 014; 55: 207-16.

3. Zeller T, Beschorner U, Pilger E et al. Pactitaxel-Coated Balloon in Infrapopliteal Arteries: 12-Month Results From the BIOLUX P-II Randomized Trial. JACC: Cardiovascular Intervention 2015;8: 1614-22.

4. Zeller T, Baumgartner I, Scheinert I et al. Drug-Eluting Balloon Versus Standard Balloon Angioplasty for infrapopliteal revascularization in critical limb ischemia: 12-Months Results from the IN.PACTDEEP Randomized Trial. Journal of The American College Cardiology 2014;64:1568-76.

10. Statistical Appendices

10.1 Reporting Conventions

Three types of endpoints will be reported: clinical/safety endpoints, core lab endpoints, and endpoints assessed by office visits.

10.1.1 Clinical/Safety Endpoints

Clinical endpoints include repeat revascularization procedures on target lesions/vessels, and major target limb amputations. Safety endpoints include major adverse event (MAE), death, and thrombosis. The event rate of the clinical/safety endpoints will be calculated on a patient level.

For each visit (or reporting time point), the event rate will be calculated using either a Kaplan-Meier curve or a cumulative incidence curve for each randomization arm.

Both of these event rate estimates use either the time to observed event, e.g. 'Days to MAE' (date of earliest MAE – date of index procedure), or time to censoring using total follow-up time after the date of the index procedure. Total follow-up time is calculated as described above in Section 7.2. Event rate estimates for death will also include vital status data collection where time is calculated using date of death, date of exit, or date of vital status assessment where the subject status is alive, whichever is later.

Estimates from either a Kaplan-Meier curve or a cumulative incidence curve will be provided for pre-specified time points. The Reporting Times and the correspondent visits are as follows:

Visit	Reporting Times
30-day	30 days post-index procedure
3-month	90 days post-index procedure

6-month	180 days post-index procedure
9-month	270 days post-index procedure
12-month	360 days post-index procedure
24-month	720 days post-index procedure
36-month	1080 days post-index procedure
48-month	1440 days post-index procedure
60-month	1800 days post-index procedure

10.1.2 Core Lab Endpoints

Core lab endpoints include the endpoints that are determined by core lab assessment (duplex ultrasound (DUS) and angiography), such as the primary endpoint Late Lumen Loss (LLL) and the secondary endpoint clinical success and functional flow assessment, etc. Core lab endpoints rely on the actual evaluable assessment. If the scheduled assessment is not completed or the data is not evaluable (i.e., not readable or non-diagnostic), it will be treated as missing value and will be excluded from the analysis.

Qualifying Angiograms at 9 months

Late lumen loss is defined as difference in MLD of the target lesion immediately after the index procedure and the MLD at 9-month angiographic follow-up or sooner in case of a TLR. For 9-month qualifying angiograms, the following steps will be followed and analysis will be performed at lesion level - target lesion assessed by Quantitative Vascular Angiography (QVA) will be qualified either at 9-month scheduled visit or at the time of a target Lesion Revascularization (TLR), whichever occurs first.

Evaluable Angiographic Assessment

Patients can be split into two categories:

1. Without any CEC adjudicated TLRs within 9-month visit
    a. If a patient had 9-month schedule angio visit with non-missing assessment, use the scheduled angio assessment;
    b. If no evaluable scheduled assessment available, use the following rules
        i. Slot evaluable angio assessments into the 9-month imaging reporting window– 211 to 330 days
        ii. If multiple assessment available in the same reporting visit, use the one closed to the target day - 270
2. With CEC adjudicated TLRs – use the angio for the assessment of the earliest TLR

Angiographic Measurements for Lumen Changes The degree of restenosis after PTA has been evaluated by a number of angiographic parameters including binary (>50%) angiographic stenosis, late lumen loss, and loss index. Traditional measurement of late lumen loss has allowed axial redistribution of the MLD

from the final to the follow-up measurement. In other words, the location of the MLD at the end of the procedure may be different at the time of follow-up angiogram. Moreover, the degree of LLL is dependent on the magnitude of acute lumen gain after the intervention.

Accordingly, the BTK Study Core Lab have designed a number of angiographic parameters for the IN.PACT BTK study that will better characterize the lumen changes that occur after DCB use. These parameters include:

Segmental Measurement Along the Entire Treated Vessel

Acute Lumen Gain: Final Procedural MLD – Pre-Procedure MLD

MLD Late Lumen Loss: Final Procedural MLD – Follow-up MLD

MLD Net Lumen Gain: Follow-up MLD – Pre-Procedure MLD

MLD Loss Index: Late Loss / Acute Gain

Follow-up % Stenosis: ((Normal Diameter – Follow-up MLD)/Normal Diameter)*100

Binary Angiographic Restenosis: % Stenosis ≥ 50%

Mean Acute Gain: Final Mean Lumen Diameter – Pre-Procedure Mean Lumen Diameter

Mean Late Lumen Loss: Final Mean Lumen Diameter – Follow-up Mean Lumen Diameter

Sub-Segmental Measurement Along the Entire Treated Vessel

In order to better characterize the lumen changes after DCB angioplasty in the Imaging Core Laboratory, we identify 10 equal sub-segments within the treated segment and perform the identical measurements outline in the above section. This method will reduce the error that occurs with the redistribution of the MLD along the length of the lesion from the final to the follow-up images

The following measurements can be used:

- Maximum Subsegment Late Number Loss (obtained from all 10 subsegments)
- Mean Subsegment Late Lumen Loss (averaged from all 10 subsegments)
- Number Subsegments with % Stenosis ≥ 50% (obtained from all 10 subsegments)
- With this rigorous methodology, the exact geometric changes that occur after drug coated angioplasty can be documented. We look forward to your comments and questions.

Please refer to IN.PACT BTK data code_definitions V1.1 for all the detailed algorithm on how to calculate the lumen change.

10.1.3 Endpoints Assessed by Office Visit

Such endpoint includes status of wound healing and functional flow assessment. This endpoint is obtained/determined through the office visit assessment or DUS. If the office visit is not completed then

this assessment will not be available, and therefore will be treated as missing value and will be excluded from the analysis.

For the assessments that are recorded on the scheduled visit forms, the scheduled visit will be used in the analyses.

For subjects who don't have any assessment for a scheduled visit (visit not done or the visit is completed but the assessment is not readable), the following rules will be used to slot the unscheduled visit assessments:

1) Assessment will be slotted into each study visit using the visit date, visit window is described as following:

Slot the visit using the following reporting windows. The study day used in the window definition is calculated as 'assessment date' minus 'index procedure date':

Study Visit	Target Day	Reporting Window
Index Procedure	Day 0	Day 0
30-day	Day 30	Study Day 1-60
3-month	Day 90	Study Day 61-135
6-month	Day 180	Study Day 136-210
9-month	Day 270	Study Day 211-330
12-month	Day 360	Study Day 331-540
24-month	Day 720	Study Day 541-900
36-month	Day 1080	Study Day 901-1260
48-month	Day 1440	Study Day 12611-1620
60-month	Day 1800	Study Day 1621+

2) The assessments with unevaluable values will be excluded from the visit slotting step

3) If multiple assessments are slotted into the same visit window, the assessment with non-missing value that is closest to the scheduled visit date (or target day for the correspondent scheduled visit described in the above table) will be used; if multiple non-missing assessments have equal distance from the scheduled visit date (or target day for the correspondent scheduled visit described in the above table), the assessment from the earlier assessment date will be used.